

Comparison of colistin–carbapenem, colistin–sulbactam, and colistin plus other antibacterial agents for the treatment of extremely drug-resistant *Acinetobacter baumannii* bloodstream infections

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Abstract The purpose of this investigation was to compare the efficacy of colistin-based therapies in extremely drug-resistant *Acinetobacter* spp. bloodstream infections (XDR-ABSI). A retrospective study was conducted in 27 tertiary-care centers from January 2009 to August 2012. The primary

end-point was 14-day survival, and the secondary end-points were clinical and microbiological outcomes. Thirty-six and 214 patients [102 (47.7 %): colistin–carbapenem (CC), 69 (32.2 %): colistin–sulbactam (CS), and 43 (20.1 %): tigecycline): colistin with other agent (CO)] received colistin

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monotherapy and colistin-based combinations, respectively. Rates of complete response/cure and 14-day survival were relatively higher, and microbiological eradication was significantly higher in the combination group. Also, the in-hospital mortality rate was significantly lower in the combination group. No significant difference was found in the clinical ($p=0.97$) and microbiological ($p=0.92$) outcomes and 14-day survival rates ($p=0.79$) between the three combination groups. Neither the timing of initial effective treatment nor the presence of any concomitant infection was significant between the three groups ($p>0.05$) and also for 14-day survival ($p>0.05$). Higher Pitt bacteremia score (PBS), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Charlson comorbidity index (CCI), and prolonged hospital and intensive care unit (ICU) stay before XDR-ABSI were significant risk factors for 14-day mortality ($p=0.02$, $p=0.0001$, $p=0.0001$, $p=0.02$, and $p=0.01$, respectively). In the multivariable analysis, PBS, age, and duration of ICU stay were independent risk factors for 14-day mortality ($p<0.0001$, $p<0.0001$, and $p=0.001$, respectively). Colistin-based combination therapy resulted in significantly higher microbiological eradication rates, relatively higher cure and 14-day survival rates, and lower in-hospital mortality compared to colistin monotherapy. CC, CS, and CO combinations for XDR-ABSI did not reveal significant differences with respect to 14-day survival and clinical or microbiological outcome before and after propensity score matching (PSM). PBS, age, and length of ICU stay were independent risk factors for 14-day mortality.

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Introduction

Extremely drug-resistant *Acinetobacter* (XDR-A) infections cause significant mortality and morbidity among hospitalized patients, particularly in intensive care units (ICUs). Extreme drug resistance is defined by susceptibility to only one or two categories [1]. The optimal treatment of infections caused by XDR-A has not yet been established [2]. Therefore, bloodstream infections (BSI) due to XDR-A has become a major therapeutic challenge in the last two decades [3]. Inappropriate treatment of *Acinetobacter* infections is associated with higher mortality [2, 4, 5]. Therefore, treatment choices should be carefully considered [2].

Although prospective, randomized controlled trials are still lacking, colistin (COL) has become the foremost therapeutic option in recent years owing to its potent bactericidal efficacy even against XDR Gram-negative bacteria [6]. While XDR-A strains are supposed to be COL-sensitive, in vitro heteroresistance has been reported during COL monotherapy [7–12]. Moreover, several combination regimens show increased in vitro activity compared to single agents and are recommended to prevent the development of resistance [8]. Due to the increasing carbapenem resistance, COL-based combinations including sulbactam, carbapenem, tigecycline, rifampicin, and aminoglycosides have become virtually the only treatment of choice in *Acinetobacter* bloodstream infections (ABSI) [9–18]. Despite studies reporting increased treatment success with COL-based combinations compared to monotherapy in extremely drug-resistant *Acinetobacter* spp.

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bloodstream infections (XDR-ABSI), clinical studies comparing different combinations are scarce. The available clinical studies usually consisted of relatively limited numbers of patients managed at a single center. Moreover, the proportion of bacteremic cases amongst all infections due to *Acinetobacter* spp. was low in small-sized studies [19, 20]. Therefore, well-designed clinical trials comparing antimicrobial combinations in the treatment of XDR-A infections are necessary. In this study, we aimed to compare the efficacy of COL monotherapy and COL-based combinations with carbapenems, sulbactams, and other antimicrobials in patients with XDR-ABSI.

Materials and methods

Study design and data collection

We conducted a retrospective, observational, multicenter study including 27 tertiary-care centers across Turkey. Patients who met the criteria for either primary or secondary XDR-ABSI and who were treated with colistin monotherapy or any of the COL-based antimicrobial combinations during the study period were included. Data regarding the demographical characteristics, clinical and laboratory features, treatment modalities, adverse events, and outcome measures were obtained from patient records or hospital databases.

Inclusion criteria

1. Isolation of XDR-A from ≥ 2 separate sets of hemoculture (peripheral veins and/or catheters) [21]
2. Treatment with a COL monotherapy intravenously for ≥ 72 h (the dosages and routes of administration being in accordance with standard institutional practice or current medical recommendations)
3. Treatment with a COL-based combination intravenously for ≥ 72 h (the dosages and routes of administration being in accordance with standard institutional practice or current medical recommendations)
4. Treatment is considered “early” or “late” if it was initiated within or after first 24 h, respectively
5. Patients could not already be on any monotherapy effective against the isolated *Acinetobacter* spp. when the culture was drawn and before colistin use
6. Patients should not have received treatment with monotherapy that is effective against XDR-A for any period of time during their treatment course
7. Only the first episode of *Acinetobacter* bacteremia and only an index culture collected from each patient were included in case of more than one bacteremic episode due to the same pathogen
8. Any concomitant infection should have to be treated appropriately and effectively

Exclusion criteria

1. Concomitant BSI with an organism other than XDR-A
2. Treatment intravenously with colistin lasting < 72 h
3. Contraindications for colistin use
4. Pregnancy
5. Age < 18 years

Definitions

Primary XDR-ABSI [21] In addition to at least two of the following criteria:

1. Fever (38 °C) or hypothermia (< 36 °C)
2. Tachypnea (respiratory rate > 24 /min)
3. Tachycardia (pulse rate > 90 /min)
4. Leukocytosis (WBC $> 12,000/\text{mm}^3$) or leukopenia (WBC $< 4,000/\text{mm}^3$)

plus at least one of the following:

1. *Acinetobacter* spp. cultured from two or more blood cultures drawn on separate occasions
2. *Acinetobacter* spp. cultured from at least one blood culture from a patient with an intravascular line, and the physician institutes appropriate antimicrobial therapy and signs and symptoms and positive laboratory results are not related to an infection at another site [21]

Secondary XDR-ABSI Isolation of XDR-A with an identical resistance pattern of the blood isolate from remote body sites (i.e., from endotracheal aspirate, urine, or wound culture).

Multidrug-resistant (MDR) “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, polymyxins) [1].

Extremely drug-resistant (XDR) “Non-susceptibility to at least one agent in all but two or more antimicrobial categories” (i.e., susceptibility to only one or two categories) [1].

Pandrug-resistant (PDR) “Non-susceptibility to all agents in all antimicrobial categories” [1].

Severity assessment scores The severity of bacteremia, patients’ clinical status, and the underlying diseases were determined by the Pitt bacteremia score (PBS) [22], the Acute Physiology and Chronic Health Evaluation II (APACHE II)

score [23, 24], and the Charlson comorbidity index (CCI), respectively [25].

Clinical outcomes

1. Complete response (cure): Recovery of all symptoms, signs, and laboratory findings of infection
2. Partial response: Disappearance of only some of the initial symptoms, signs, and laboratory findings of infection (fever or hypothermia, tachypnea, tachycardia, leukocytosis or leukopenia, elevated acute-phase reactants such as CRP, procalcitonin), including the condition not fulfilling all the requirements for complete response
3. Treatment failure: Persistence or worsening of all symptoms and signs of infection despite antimicrobial treatment

Microbiological outcome Microbiological eradication of *Acinetobacter* spp. in any control blood cultures.

The primary end-point was survival/death on the 14th day of treatment. The secondary end-points were clinical outcome, microbiological outcome, or colistin toxicity/adverse effect (nephrotoxicity, neurotoxicity).

Effective therapy Therapy that will result in clinical cure and microbiological eradication.

Normal renal function Baseline serum creatinine (SCR) \leq 1.3 mg/dl (without complicated DM, chronic kidney disease, nephrotoxic drug use, hypovolemia). **Nephrotoxicity:** According to the RIFLE criteria [26], \geq 50 % increase in baseline SCR or requirement of renal replacement therapy. **Neurotoxicity:** Development of peripheral and orofacial paresthesias, visual disturbances, vertigo, irritability, mental confusion, ataxia, seizures, and any neurologic impairment defined by a neurologist as neurotoxicity that did not pre-exist at the time of the start of therapy [27].

Microbiological tests

The identification of *Acinetobacter baumannii* isolated from blood samples was made by conventional methods and automated systems. Antimicrobial susceptibility was tested with the disk diffusion and agar dilution methods at the participating hospitals. The minimum inhibitory concentration (MIC) values were determined by the Etest, and the results were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) criteria [“Performance standards for antimicrobial disk susceptibility tests; Approved standard—Eleventh edition (M02-A11)”, “Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; Approved standard—Ninth edition (M07-A9)”, and “Performance standards for antimicrobial susceptibility testing; Twenty-second informational supplement (M100-S22)”];

CLSI, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, USA, 2012].

Ethical statement/approval

This study was approved by the Institutional Review Board of Kartal Dr. Lutfi Kirdar Education and Research Hospital.

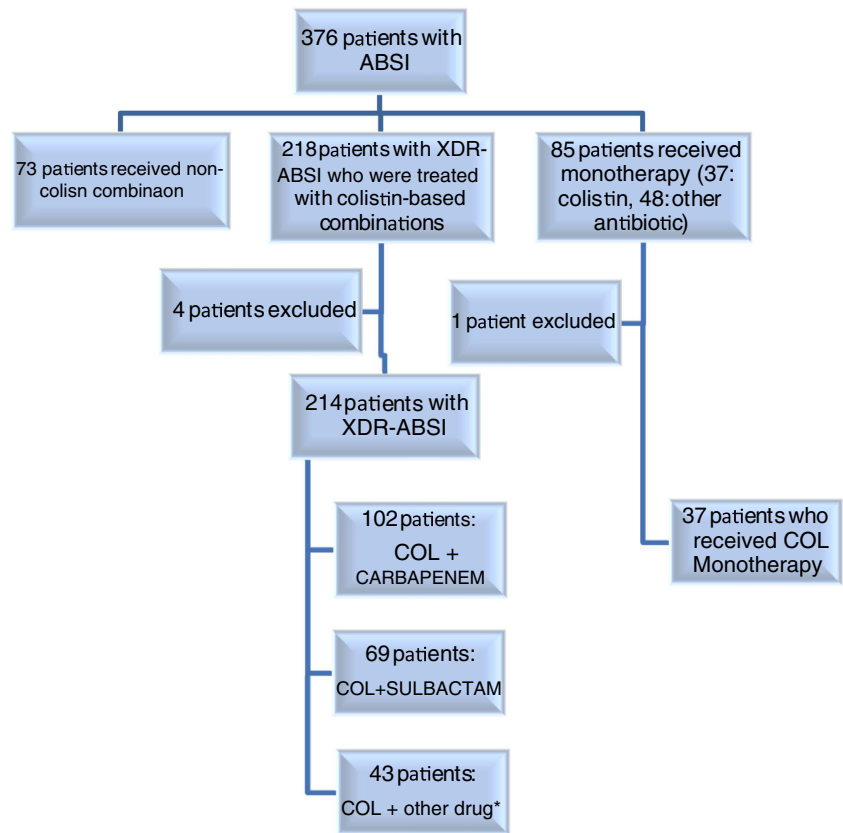
Statistical analyses

For all statistical analyses, the SPSS 17.0 software package (SPSS Inc., Chicago, IL, USA) was used. In a general comparison, categorical variables were compared by the χ^2 or Fisher’s exact test, and continuous variables were tested with Student’s *t*-test or one-way analysis of variance (ANOVA), as appropriate. In the survival analyses, the survival rates for each treatment group were determined by the Kaplan–Meier method. In the univariate analysis, the survival rates of the groups were tested by the log-rank χ^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 XDR-ABSI. Propensity score matching (PSM) was performed to adjust for selection bias. The propensity score (PS) was estimated by multinomial logistic regression including all prognostic factors related to the treatment allocation. Patients who had similar PS in three different groups were matched by using the nearest neighbor matching method. Some patients who had PS < 0.35 and PS > 0.7 were excluded from groups to form the new sample. After PSM, groups had similar characteristics in risk factors. The entire analysis was repeated after PSM. A *p*-value < 0.05 was considered to be statistically significant.

Results

Out of the pooled data of 376 patients who were treated for ABSI in 27 tertiary-care centers in seven provinces of Turkey from January 2009 to August 2012, a total of 37 patients who received COL monotherapy and 218 patients who received COL-based combinations were enrolled in this study. Four patients in the combination therapy group and one patient in the monotherapy group who did not meet the inclusion criteria or had inadequate data were excluded (Fig. 1). Thirty-six (21, 58 % male, mean age 58.3 \pm 20.5 years) patients received COL monotherapy. Among a total of 214 patients who received COL-based combination therapy, 141 (65.9 %) were male and the mean age was 59.1 \pm 19.6 years. The mean durations of in-hospital follow-up were 45.8 \pm 37.8 (range: 9–223) days and 56.9 (range: 5–497) days in the COL monotherapy and COL-based combination groups, respectively. The baseline

Fig. 1 A consort diagram showing the number of included and excluded patients



characteristics of the patients, mean durations of hospitalization and ICU stay before the diagnosis of ABSI, mean CCI, mean APACHE II score, and mean PBS in the monotherapy and combination therapy groups were similar (Table 1).

Among the patients in the COL-based combination group, 102 (47.7%), 69 (32.2%), and 43 (20.1%) received colistin–carbapenem (CC) (47: imipenem 4×500 mg, 43: meropenem 3×1 g, 12: doripenem 3×500 mg), colistin–sulbactam (CS) (in the form of ampicillin–sulbactam 4×3 g or sulbactam 4×1.5 g), and COL plus other antimicrobial agents (CO) [24: tigecycline (TIG) 2×50 mg after an initial 100-mg loading dose, 7: amikacin 1×1,000 mg, 3: netilmicin 3×2 mg/kg, 3: gentamicin 2×160 mg; in total: 13 aminoglycoside (AG), 3: rifampicin (RIF) 1×600 mg, 3: piperacillin–tazobactam 3×4.5 g], respectively. A loading dose for colistin had not been recommended at the time the study was conducted (the Sanford guide modified the colistin dosage schedule on October 08, 2012), so in our retrospective study, none of the patients had received a loading dose of colistin. Colistin daily dose in patients with normal renal function was 5 mg colistin base activity/kg/day divided into 2–3 doses in each treatment group. There were no differences in the MICs of the isolates against colistin and other antibiotics between the different treatment groups. As the number of patients receiving any of the “other” drugs in combination with COL was low in each group, we grouped them into a single group.

First of all, we compared the efficacy of colistin monotherapy and colistin-based antimicrobial combinations in patients with ABSI who had similar baseline characteristics, CCI, PBS, and APACHE II scores. The rates of complete response/cure and 14-day survival were relatively higher in the combination group compared to the monotherapy group (46.3% vs. 30.6% and 68.2% vs. 55.5%, respectively), and microbiological eradication was significantly much higher in the combination group than the monotherapy group (79.9% vs. 55.6%, $p=0.001$). Also, the in-hospital mortality rate was significantly lower in the combination group compared to the monotherapy group (52.3% vs. 72.2%, $p=0.03$) (Table 1). Therefore, we compared the three different combination groups with each other in terms of efficacy.

The baseline patient characteristics, bacteremia type (primary, secondary, or catheter-related BSI), and outcomes of 214 cases with XDR-ABSI, according to the three different combination modalities, are demonstrated in Table 2. The mean duration of hemoculture positivity was 5.29 ± 3.21 days, and it did not differ significantly between the three groups ($p=0.27$). Catheters had been withdrawn in 28 (96.5%) cases with catheter-related BSI. All MIC values of colistin for *Acinetobacter baumannii* were less than 1 µg/ml.

A total of 128 (59%) of the patients had another concomitant infection. The presence of any concomitant infection did not differ significantly between the three groups ($p=0.17$).

Table 1 Baseline demographic and clinical characteristics and outcomes of 214 patients with extremely drug-resistant *Acinetobacter* spp. bloodstream infections (XDR-ABSI) who received colistin-based combination therapy and 36 patients who received colistin monotherapy

Characteristic/variable	Colistin combination group, n (%)	Colistin monotherapy group, n (%)	<i>p</i> -Value
Total (<i>n</i>)	214	36	
Age (mean ± SD) (years)	59.1±19.6	58.3±20.5	0.81
Gender (male)	141 (65)	21 (58)	0.46
Hospital stay prior to XDR-ABSI (mean ± SD, days)	23.9±21.9	22.3±19.9	0.69
ICU stay prior to XDR-ABSI (mean ± SD, days)	19.1±19.3	18.9±20.8	0.96
Pitt bacteremia score (mean ± SD)	7.1±3.6	6.8±2.9	0.62
APACHE II score ^a (mean ± SD)	18.6±6.9	17.9±7.1	0.82
Charlson comorbidity index (mean ± SD)	3.3±2.2	3.5±2.2	0.55
Concomitant other infection	128 (59)	20 (56)	0.63
Initiation of effective therapy			0.13
Early (within 24 h)	152 (71)	21 (58.3)	
Late (after 24 h)	62 (29)	15 (41.7)	
Nephrotoxicity	36 (21.8)	9 (25)	0.88
Neurotoxicity ^b			
Present	3 (1.4)	0 (0)	
Unconscious/pharmacologic sedation	211 (98.6)	36 (100)	
Clinical outcome			0.19
Complete response/cure	99 (46.3)	11 (30.6)	
Partial response/improvement	68 (31.8)	16 (44.4)	
No response/failure	47 (22)	9 (25)	
Microbiologic outcome			0.001
Eradication present	171 (79.9)	20 (55.6)	
Redundant	43 (20.1)	16 (44.4)	
14-day survival	146 (68.2)	20 (55.5)	0.14
In-hospital crude mortality	112 (52.3)	26 (72.2)	0.03

Data are presented as number (%) of patients or mean value ± standard deviation (SD)

XDR-ABSI extremely drug-resistant *Acinetobacter* spp. bloodstream infections

^a The APACHE II score was calculated in 169 patients in the combination group and in all patients in the monotherapy group

^b Neurotoxicity was reported in only three patients; therefore, the *p*-value was not taken into consideration

The primary sources of bacteremia are summarized in Table 3. The proportion of secondary bacteremia did not differ significantly between the three treatment groups (*p*=0.3).

Effective antimicrobial treatment was initiated in the first 24 h of infection (i.e., early) in 152 (71 %) and after 24 h (i.e., late) in 62 (29 %) of the patients. Only 36 (16.7 %) of the patients developed nephrotoxicity under COL treatment; the COL dose was decreased in 29 (13.6 %) and discontinued in 7 (3 %). Because of unconsciousness/pharmacological sedation in 118 (55 %) patients, the neurological status could not be evaluated. Only 3 (0.14 %) patients among those with assessable neurological status had any neurotoxicity, but none of them had discontinuation of colistin therapy. The all-cause in-hospital crude mortality was 52.3 %. The rates of all-cause mortality ranged from 46.4 to 55.8 % in the three groups, being relatively lower in the CS group, but they were not statistically different between the groups (*p*=0.44).

Prolonged hospital and ICU stay before XDR-ABSI were significant risk factors for 14-day mortality (*p*=0.02 and *p*=0.01, respectively). Neither the timing of initial effective treatment nor the presence of any concomitant infection was significant between the three combination groups (*p*=0.38 and *p*=0.17, respectively) or for 14-day survival (*p*=0.7 and *p*=0.8, respectively). No significant difference was observed regarding the clinical (*p*=0.97) and microbiological (*p*=0.92) outcomes and 14-day survival rates (*p*=0.79) between the three groups. The PBS, APACHE II score (calculated in 169 patients), and CCI as risk-adjustment severity parameters were not significantly different between the three groups, while higher PBS, APACHE II score, and CCI were related to higher 14-day mortality (*p*=0.02, *p*=0.0001, and *p*=0.0001, respectively) in the univariate analysis. Gender, concomitant other infection, initiation time of antibiotic treatment, nephrotoxicity, and neurotoxicity were not significant for 14-day survival

Table 2 Demographic and clinical characteristics and outcomes of 214 patients with extremely drug-resistant *Acinetobacter* spp. bloodstream infections (XDR-ABSI), according to the three different combination treatment modalities

Characteristic/variable	Colistin–carbapenem group, <i>n</i> (%)	Colistin–sulbactam group, <i>n</i> (%)	Colistin plus other agent group, <i>n</i> (%)	<i>p</i> -Value
Total, <i>n</i>	102	69	43	
Age (mean ± SD) (years)	58.94±19.8	58.2±20	60.9±19.1	0.77
Gender (male)	67 (65.7)	50 (72.5)	24 (55.8)	0.19
Hospital stay prior to XDR-ABSI (mean ± SD, days)	24.27±22.7	20.9±16.7	27.8±26.7	0.25
ICU stay prior to XDR-ABSI (mean ± SD, days)	20.5±23	18.3±15.9	17±13.5	0.58
Pitt bacteremia score (mean ± SD)	7.23±3.6	7±3.5	6.9±3.7	0.85
APACHE II score ^a (mean ± SD)	18.2±7.1	17.2±8.1	19.2±8.4	0.48
Charlson comorbidity index (mean ± SD)	3.31±2.1	3.16±2.1	3.58±2.5	0.62
Primary bacteremia	43 (42.2)	37 (53.6)	17 (39.5)	0.28
Secondary bacteremia	44 (43.1)	23 (33.3)	20 (46.5)	0.3
Catheter-related BSI	15 (14.7)	9 (13.1)	6 (14)	0.33
Concomitant other infection	59 (57.8)	38 (55)	31 (72)	0.17
Initiation of effective therapy				
Early (within 24 h)	77 (75.5)	46 (66.7)	29 (67.4)	0.38
Late (after 24 h)	25 (24.5)	23 (33.3)	14 (32.6)	
Nephrotoxicity	16 (22.8)	10 (19.6)	10 (33.3)	0.36
Neurotoxicity ^b				0.16
Present	3 (3)	0 (0)	0 (0)	
Unconscious/pharmacologic sedation	59 (57.8)	40 (58)	19 (44.2)	
Clinical outcome				0.97
Complete response/cure	50 (49)	32 (46.4)	17 (39.5)	
Partial response/improvement	28 (27.5)	23 (33.3)	17 (39.5)	
No response/failure	24 (23.5)	14 (17.4)	9 (21)	
Microbiologic outcome				0.92
Control hemoculture obtained	95 (93)	62 (90)	39 (90.7)	
Eradication present	77 (81)	49 (79)	32 (82)	
Redundant	18 (18.9)	13 (20.9)	7 (17.9)	
14-day survival	72 (70.6)	47 (68.1)	27 (62.8)	0.79
In-hospital crude mortality	56 (55)	32 (46.4)	24 (55.8)	0.44

Data are presented as number (%) of patients or mean value ± standard deviation (SD)

XDR-ABSI extremely drug-resistant *Acinetobacter* spp. bloodstream infections; BSI: bloodstream infection

^a The APACHE II score was calculated in 169 patients

^b Neurotoxicity was reported in only three patients; therefore *p*-value was not taken into consideration

(all $p > 0.05$) (Table 4). Multivariable analysis showed that PBS, age, and duration of ICU stay before XDR-ABSI were independent risk factors for 14-day mortality in patients with XDR-ABSI ($p < 0.0001$, $p < 0.0001$, and $p = 0.001$ respectively) (Table 5).

After PSM, 152 (78: colistin–carbapenem group, 43: colistin–sulbactam, 31: colistin plus other agent) patients remained in our data set and we repeated the survival analysis. The rates of 14-day survival, clinical outcome, microbiological eradication, and the independent risk factors for 14-day mortality did not change after PSM. The results before and after PSM are shown in Tables 4, 5, and 6. Only the length of

hospital stay, which was significant for 14-day survival in the univariate analysis before PSM, became insignificant after PSM. However, the independent risk factors for 14-day mortality did not change after PSM in the multivariable analysis.

Discussion

As there has been a diversity of definitions in publications regarding MDR and PDR *Acinetobacter* and *Pseudomonas* [28], an international proposal for definitions of MDR, XDR, and PDR bacteria was published in 2012 [1]. We preferred to

Table 3 Primary sources of secondary bacteremia in the three different treatment groups

Primary source of infection	CC group, n (%)	CS group, n (%)	CO group, n (%)
VAP	33 (32.3)	14 (20.2)	10 (23.2)
Urinary system	2	2	5
Surgical site/skin and skin structures infection	4	2	–
VAP+urinary tract infection	1	2	3
VAP+catheter-related infection	1	1	1
Intra-abdominal infection	2	1	–
Others	1 ^a	1 ^b	1 ^c
Total	44 (43.1)	23 (33.3)	20 (46.5)

CC colistin–carbapenem; CS colistin–sulbactam; CO colistin plus other antimicrobial agent; VAP ventilator-associated pneumonia

^a Meningitis

^b Arthritis

^c Anorectal abscess

use the updated definitions of resistance in this manuscript, although the majority of the references we have cited used previous MDR definitions regarding resistance, as they were published before 2012.

Colistin has become the first-line treatment choice in XDR-ABSI. Although there is no proof that combination therapies including COL are superior to COL monotherapy in the treatment of XDR-ABSI, due to heteroresistance during COL monotherapy, rapid selection of resistance in some strains, and lower clinical efficacy, COL-based combinations are widely recommended [10–19]. This was confirmed in the first-step analysis of the present study, and colistin-based combinations were found to be significantly superior to

colistin monotherapy in terms of efficacy and survival outcomes. We further compared the efficacies of three different combination groups.

Clinical studies comparing different combinations are very scarce in the literature. Data regarding synergy or combination of antimicrobials rely on in vitro or animal studies, whereas the results of in vitro and animal studies may not translate into clinical practice [29]. Even the same antimicrobial combinations have been reported to have different results, causing conflict [30, 31]. Despite a few studies reporting no benefit from combinations [32], the majority of studies highlight the superiority of combination therapy compared to monotherapy [10–19]. In a recently published randomized, clinical trial, although the all-cause 30-day mortality, infection-related death, and length of hospitalization were not statistically significant between the COL monotherapy group and the COL–rifampicin combination group, a significant increase of the microbiologic eradication rate was observed in the combination group [33]. The authors concluded that “increased rate of *A. baumannii* eradication with combination therapy could still imply a clinical benefit”. In addition, a commentary on this article has recently been published by Pogue and Kaye [34]. The authors concluded that, for the treatment of invasive infections caused by *A. baumannii*, combination therapy could not definitely be stated as unwarranted regarding the aforementioned study, but rifampicin was not an ideal agent to be combined with colistin. Furthermore, monotherapy leads to the development of high-level resistance through the overexpression of efflux pumps. The colistin–rifampicin combination has been shown to prevent the development of resistant mutants with available in vitro and in vivo data [35]. Also, in our study, the microbiologic eradication rate was significantly higher in the combination group compared to the monotherapy group, but it was not statistically different between the

Table 4 Univariate analysis of the risk factors for 14-day survival among patients with extremely drug-resistant *Acinetobacter* spp. bloodstream infections (XDR-ABSI), before and after propensity score matching (PSM)

Risk factors	Before PSM		After PSM	
	HR (95 % CI)	<i>p</i> -Value	HR (95 % CI)	<i>p</i> -Value
Age	1.04 (1.02–1.05)	<0.0001	1 (1.02–1.06)	<0.0001
Gender	0.88 (0.59–1.32)	0.111	0.89 (0.75–1.2)	0.4
Hospital stay prior to XDR-ABSI	1.2 (1.1–1.3)	0.02	1.2 (1.1–1.3)	0.2
ICU stay prior to XDR-ABSI	1.3 (1.2–1.4)	0.01	1.3 (1.2–1.4)	0.042
Pitt bacteremia score	1.19 (1.1–1.29)	0.02	1.2 (1.1–1.4)	<0.0001
APACHE II score	1.05 (1.05–1.08)	<0.0001	1.06 (1.02–1.1)	0.007
Charlson comorbidity index	1.2 (1.1–1.3)	<0.0001	1.2 (1.03–1.3)	0.017
Early vs. late therapy	0.76 (0.47–1.22)	0.7	0.78 (0.49–1.24)	0.46
Concomitant other infection	1.26 (0.84–1.91)	0.8	1.2 (0.9–1.7)	0.5

PSM propensity score matching; HR hazard ratio; CI confidence interval; XDR-ABSI multidrug-resistant *Acinetobacter* spp. bloodstream infections; ICU intensive care unit

Table 5 Multivariable stepwise Cox regression analysis of the risk factors for 14-day mortality among patients with extremely drug-resistant *Acinetobacter* spp. bloodstream infections XDR-ABSI) in order of importance, before and after propensity score matching (PSM)

Risk factors	Before PSM		After PSM	
	HR (95 % CI)	<i>p</i> -Value	HR (95 % CI)	<i>p</i> -Value
Pitt bacteremia score	1.24 (1.1–1.35)	<0.0001	1.23 (1.12–1.35)	<0.0001
Age	1.04 (1.02–1.06)	<0.0001	1.04 (1.02–1.06)	<0.0001
Length of stay in ICU	1.37 (1.35–1.39)	0.001	1.37 (1.35–1.39)	0.001

PSM propensity score matching; HR hazard ratio; CI confidence interval; ICU intensive care unit

three combination groups. Only three patients had received a colistin–rifampicin combination.

As the literature lacks clinical data about better and more effective combinations, we further designed our study to reply to the question: Which combination would be clinically optimal in the treatment of XDR-ABSI? This multicenter study included quite a large number of patients with XDR-ABSI, and the study groups were adjusted for clinical severity indices and comorbidities. Furthermore, PSM analysis was performed to adjust for all confounding variables.

In clinical practice, the safety profile, potential to induce resistance selection or collateral damage, cost of drug(s), and, also, the local antimicrobial usage strategy should be taken into consideration while deciding on combination therapy. Despite recommendations on the use of carbapenem-based combinations in the treatment of MDR-ABSI because of synergistic activity, the widespread use of carbapenems has been reported to cause increased selection of carbapenem-resistant strains [36]. Carbapenem use had been significantly associated with increased incidence of carbapenem-resistant *A. baumannii* [37]. A very recently published study has reported a 2.24-fold decrease in the prevalence of infections due to MDR *A. baumannii* strains achieved after implementing a policy of restricted carbapenem use in the ICU [38]. In

addition to resistance selection, widespread carbapenem use may result in more frequent adverse effects/collateral damage and increased therapeutic costs. When the indifferent therapeutic results of the three COL-based combination groups in our study are considered, a carbapenem-sparing regimen including an antimicrobial agent with the lowest cost and risk of collateral damage should be preferred.

Sulbactam has moderate bacteriostatic activity, even against imipenem-resistant *Acinetobacter* isolates. Though not recommended as monotherapy in severe infections [39], it is a reasonable option for combined regimens. The COL–sulbactam combination revealed high in vitro synergistic activity against imipenem-resistant *Acinetobacter*, particularly in COL-resistant strains [40].

The CO group in our study included combinations of COL–TIG, COL–AG, and COL–RIF. The COL–TIG combination (24/43) has shown synergistic activity against XDR *A. baumannii* strains in in vitro studies [41]. Nevertheless, due to low plasma concentrations, TIG is disadvantageous in bacteremic patients.

When the outcomes and 14-day survival rates of combined regimens were evaluated separately or cumulatively, CC and CS combinations did not differ significantly. For the CO group, due to the relatively low numbers of cases in each

Table 6 Outcomes of 152 patients with extremely drug-resistant *Acinetobacter* spp. bloodstream infections (XDR-ABSI) after propensity score matching (PSM) analysis, according to the three different combination treatment modalities

Characteristic/variable	Colistin–carbapenem group, <i>n</i> (%)	Colistin–sulbactam group, <i>n</i> (%)	Colistin plus other agent group, <i>n</i> (%)	<i>p</i> -Value
Total, <i>n</i>	78	43	31	
Clinical outcome				0.93
Complete response/cure	40 (51.3)	25 (58.1)	12 (38.7)	
Partial response/improvement	22 (28.2)	8 (18.6)	12 (38.7)	
No response/failure	16 (20.5)	10 (23.3)	7 (22.6)	
Microbiologic outcome				0.48
Eradication present	64 (82)	38 (88.4)	27 (87)	
Redundant	14 (17.9)	5 (11.6)	4 (12.9)	
14-day survival	55 (70.5)	29 (67.4)	17 (54.8)	0.49
In-hospital crude mortality	38 (48.7)	19 (44.2)	19 (61.3)	0.33

treatment subgroup, it is difficult to comment on the treatment outcomes. In vitro studies including those combinations also reported similar results [10–12, 21, 39].

The presence of confounding factors such as various underlying diseases or severities of the infection due to patient factors, delays in diagnostic procedures, and onset of proper treatment were significant impediments that complicate comparing the efficacies of combined antimicrobial regimens in XDR-ABSI. Concerning the major importance of these confounders, we have made risk/severity adjustments, as the mean values of the CCI, PBS, and APACHE II score did not significantly differ between monotherapy, the combination therapy group as a whole, or the three different combination groups.

In the univariate analysis of predictors of 14-day survival, the age of the patient, PBS, CCI, APACHE II score, and length of stay in hospital and in the ICU before the diagnosis of XDR-ABSI were found to be significant. In the multivariable analysis, age, PBS, and length of ICU stay were independent predictors of 14-day survival. Older age (>50 years) has been reported to be significantly associated with increased mortality [42]. In similar clinical studies, the CCI, APACHE II score, and PBS had been used for adjustment of the severity of underlying comorbidities, clinical status, and bacteremia, and all severity assessment tools have been reported as independent risk factors for mortality [25, 43]. High APACHE II score (≥ 21) in patients with MDR-ABSI has been reported to be an independent risk factor for 14-/30-day or in-hospital mortality in various studies [24, 32, 37].

The all-cause in-hospital mortality is usually high in patients with MDR- and/or XDR-ABSI due to the coexistence of comorbidities and high clinical severity scores. In our study, the duration of hospital and ICU stay of patients before the diagnosis of XDR-ABSI was significantly associated with survival, as MDR- and XDR-ABSI usually develops in patients with longer durations of hospital or ICU stay and prolongs the duration of hospital stay even more. The length of hospital stay before the diagnosis of bacteremia has been reported to be longer in patients with carbapenem-resistant *Acinetobacter* bacteremia and has been a predictor of mortality [44].

Before making any conclusions, we should declare some limitations of our study. Its retrospective design seems to be the basic limitation of our study. We were not able to measure the concentrations of formed colistin and other antibiotics in the plasma of these patients. There might be suboptimal exposure to the antibiotics in blood. Colistin population analysis profiles of these isolates were not examined. Also, pharmacokinetics and pharmacodynamics must be considered when examining the efficacy of antibiotic combinations. Other limitations were the presence of concomitant foci of infections other than XDR-ABSI and the use of other drugs for concomitant infections in some patients, unstandardized doses of colistin use, and inadequate data about effective source control because of the retrospective design. Because of ethical

concerns, it is very difficult to conduct prospective clinical trials on this issue. Besides, we think that the results of our study, which included a remarkable number of cases, would provide significant benefits in making a decision on the therapeutic choices in XDR-ABSI. To our knowledge, this is the first study comparing monotherapy and combination therapy where three severity assessment tools (CCI, APACHE II score, and PBS) have been used for the adjustment of clinical severities of patients. Furthermore, PSM analysis was performed to adjust for all confounding variables.

In conclusion, the rates of cure and 14-day survival were relatively higher in the combination group compared to the monotherapy group, and the microbiological eradication rate was significantly much higher in the combination group than the monotherapy group. Also, the in-hospital crude mortality rate was significantly lower in the combination group compared to the monotherapy group. Colistin-based combinations with CC, CS, and CO for XDR-ABSI did not reveal significant differences with respect to the 14-day survival, clinical response, or microbiological outcome. PBS, age, and length of ICU stay were found to be independent risk factors for 14-day mortality before and after PSM. Although the outcomes of the combination treatment groups did not differ significantly, colistin–sulbactam may be a suggestible and more favorable combination. Carbapenem-sparing combinations may be preferable in the treatment of *Acinetobacter* infections to prevent collateral damage, particularly resistance selection and to decrease the prevalence of *Acinetobacter* infections. Well-designed controlled prospective clinical trials are needed in order to determine the optimal antimicrobial therapy in critically ill patients with XDR-ABSI.

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