Colistin and Rifampicin Compared With Colistin Alone for the Treatment of Serious Infections Due to Extensively Drug-Resistant *Acinetobacter baumannii*: A Multicenter, Randomized Clinical Trial

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(See the Editorial Commentary by Gauthier on pages 359–61.)

Background. Extensively drug-resistant (XDR) *Acinetobacter baumannii* may cause serious infections in critically ill patients. Colistin often remains the only therapeutic option. Addition of rifampicin to colistin may be synergistic in vitro. In this study, we assessed whether the combination of colistin and rifampicin reduced the mortality of XDR *A. baumannii* infections compared to colistin alone.

Methods. This multicenter, parallel, randomized, open-label clinical trial enrolled 210 patients with life-threatening infections due to XDR *A. baumannii* from intensive care units of 5 tertiary care hospitals. Patients were randomly allocated (1:1) to either colistin alone, 2 MU every 8 hours intravenously, or colistin (as above), plus rifampicin 600 mg every 12 hours intravenously. The primary end point was overall 30-day mortality. Secondary end points were infection-related death, microbiologic eradication, and hospitalization length.

Results. Death within 30 days from randomization occurred in 90 (43%) subjects, without difference between treatment arms ($P = .95$). This was confirmed by multivariable analysis (odds ratio, 0.88 [95% confidence interval, .46–1.69], $P = .71$). A significant increase of microbiologic eradication rate was observed in the colistin plus rifampicin arm ($P = .034$). No difference was observed for infection-related death and length of hospitalization.

Conclusions. In serious XDR *A. baumannii* infections, 30-day mortality is not reduced by addition of rifampicin to colistin. These results indicate that, at present, rifampicin should not be routinely combined with colistin in clinical practice. The increased rate of *A. baumannii* eradication with combination treatment could still imply a clinical benefit.

Clinical Trials Registration. NCT01577862.

Keywords. mortality; ventilator-associated pneumonia; antimicrobial therapy; treatment efficacy; treatment safety.

Extensively drug-resistant (XDR) *Acinetobacter baumannii* (Acb) [1] is increasingly recognized as an etiologic agent of nosocomial infections associated with high mortality in critically ill patients [2–5].

Epidemic XDR isolates of Acb may show resistance to almost all classes of antimicrobials, including carbapenems [4, 6, 7]. In these infections, the only viable therapeutic option may be represented by colistin [8–11], despite its relatively low intrinsic efficacy, a suboptimal lung penetration, and the risk for significant renal toxicity [6, 12–15]. However, even with colistin treatment, mortality remains high [16].

Synergy against XDR Acb was shown in both in vitro [17–19] and experimental studies [20, 21] when colistin was combined with rifampicin, prompting their combined clinical use in XDR Acb infections. Three uncontrolled clinical studies have assessed the safety and clinical efficacy of the colistin-rifampicin combination, showing very high overall response rates, without major adverse events [22–24]. By altering membrane permeability, colistin may facilitate rifampicin entry within the bacterial cell and therefore enhance its killing activity [25, 26]. However, no proof of superiority of the colistin-rifampicin combination over colistin monotherapy was provided.

Therefore, we performed a randomized controlled trial to assess whether the addition of rifampicin to colistin reduced the mortality of patients with life-threatening infections due to XDR Acb compared to colistin alone.

METHODS

Study Design

This was a multicenter, open-label, parallel, phase III, randomized clinical trial. Patients were randomly allocated to either colistin (control arm) or colistin plus rifampicin (experimental arm) on a 1:1 basis. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and of Good Clinical Practice. The ethics committee of each participating institution approved the study. The study was designed by the academic investigators and was approved, endorsed, and funded by the Italian Medicines Agency. All patients provided written informed consent. In case of patient unconsciousness, the informed consent was obtained by his/her legal representative.

Participants

Enrolled patients were hospitalized in the intensive care units (ICUs) of 5 large Italian clinical centers. Subjects were categorized as having been admitted initially to the ICU or transferred to the ICU from medical or surgical wards. Adult subjects (>18 years) were eligible for the study if they had microbiologic evidence of a life-threatening nosocomial infection due to XDR Acb [1] susceptible to colistin (minimum inhibitory concentration [MIC], ≤2 mg/L). Infections included hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), bloodstream infection (BSI), and complicated intra-abdominal infection (cIAI). Severity of the underlying illnesses was assessed

by the Simplified Acute Physiology Score (SAPS) II [27]. Co-morbidities were assessed by the Charlson index [28].

Exclusion criteria were previous treatment with colistin or rifampicin during the index hospitalization, reported hypersensitivity to either study drug, or significant liver dysfunction (defined by serum conjugated bilirubin >3 mg/dL). Enrollment was done irrespective of the strain MIC of rifampicin, as this is not routinely tested in clinical microbiology practice. Rifampicin MICs were tested subsequently for all baseline and follow-up strains in a centralized laboratory, and results were included in the multivariable analysis of treatment outcome.

Definitions

"Extensively drug resistant" was defined as resistance to carbapenems (MIC ≥16 mg/L) and to all other antimicrobial drug classes, except colistin [1]. HAP/VAP was diagnosed as an evolving infiltrate on chest radiograph with either fever or leukocytosis/leukopenia or purulent respiratory secretions with positive quantitative culture from tracheal aspirate (at least 10^6 colony-forming units [CFU]/mL) or bronchoalveolar lavage (at least 10^4 CFU/mL) [29]. BSI was defined as positive blood cultures for Acb in the presence of systemic inflammatory signs [30]. Complicated intra-abdominal infections were diagnosed as a positive Acb culture of purulent exudate from abdominal collections, associated with a systemic inflammation [31].

Infection-related death was defined as death occurring in the presence of persistent clinical signs and microbiologic evidence of Acb infection (persistent pneumonia, abdominal discharge, septic shock, persistently positive cultures, raised inflammatory markers). Microbiologic eradication was defined as disappearance of Acb in all follow-up cultures from the primary source of infection (ie, blood, bronchoalveolar lavage, or bronchial aspirate, drainage fluids) during treatment.

Clinical cure was defined as disappearance of symptoms and signs of infection, irrespective of Acb eradication at the site of infection. Therapeutic failure was defined as worsening at any time or no improvement of clinical conditions by day 21 of therapy in the presence of persistently positive Acb cultures. Renal toxicity was defined according to the RIFLE (risk, injury, failure, loss, end-stage renal disease) criteria [32, 33] in terms of changes of serum creatinine levels relative to baseline. Hepatic toxicity was defined as an increase of conjugated bilirubin >3 mg/dL.

Interventions

The control arm received colistin alone, available in Italy as colistimethate sodium (Colimicina, UCB Pharma SpA, Milan, Italy), at an initial dose of 2 million units (equal to 160 mg of colistimethate sodium) every 8 hours intravenously or according to renal function (Supplementary Table 1). In addition to colistin, at the same dose, the experimental arm received rifampicin, 600 mg every 12 hours intravenously. Treatment

assignment was not blinded because of the pragmatic nature of the study. Treatment had to be administered for at least 10 days and up to a maximum of 21 days. Length of treatment was determined by the physician in charge. Drug dosages were adjusted based on actual renal and liver function according to a predefined protocol (Supplementary Table 1) [9–12].

Treatment was discontinued in case of clinical cure (with or without microbiologic eradication), therapeutic failure, occurrence of severe renal or liver toxicity, or patient death. Coinfections were treated by the physician in charge according to current guidelines [29–31]. Except for rifampicin in the control group, any other drug was allowed, where needed. Aerosolized colistin was not allowed in any of the 2 treatment arms and no patient received it at any time during the study. Retrieval of clinical, laboratory, and microbiologic data, including concomitant or superimposed pathogens, was performed at days 1, 4, 7, 11, 14, 21, and 30 after randomization.

All isolates were originally identified as *A. baumannii–Acinetobacter calcoaceticus* complex using the VITEK 2 system (bioMérieux, Marcy l'Étoile, France). Species identification was confirmed by amplification of the $bla_{OXA-51-like}$ gene and by a trilocus sequencing typing protocol specific for Acb [34]. All strains prospectively isolated underwent routine antimicrobial susceptibility testing, including determination of colistin MIC. Subsequently, all strains were sent to the coordinating center reference laboratory and stored for further use. Rifampicin susceptibility was determined in this laboratory by the microdilution method in Mueller–Hinton broth II according to Clinical and Laboratory Standards Institute guidelines [35]. In the absence of internationally recognized breakpoints, Acb resistance to rifampicin was defined as an MIC >16 mg/L according to the recommendations of the French Society of Microbiology [36] and our previous studies [37].

Outcomes

The primary study outcome was 30-day mortality, defined as death for any cause occurring within 30 days from randomization. Length of follow-up was at least 30 days from randomization in all patients. Follow-up was extended to the end of the hospitalization when this occurred later than 30 days.
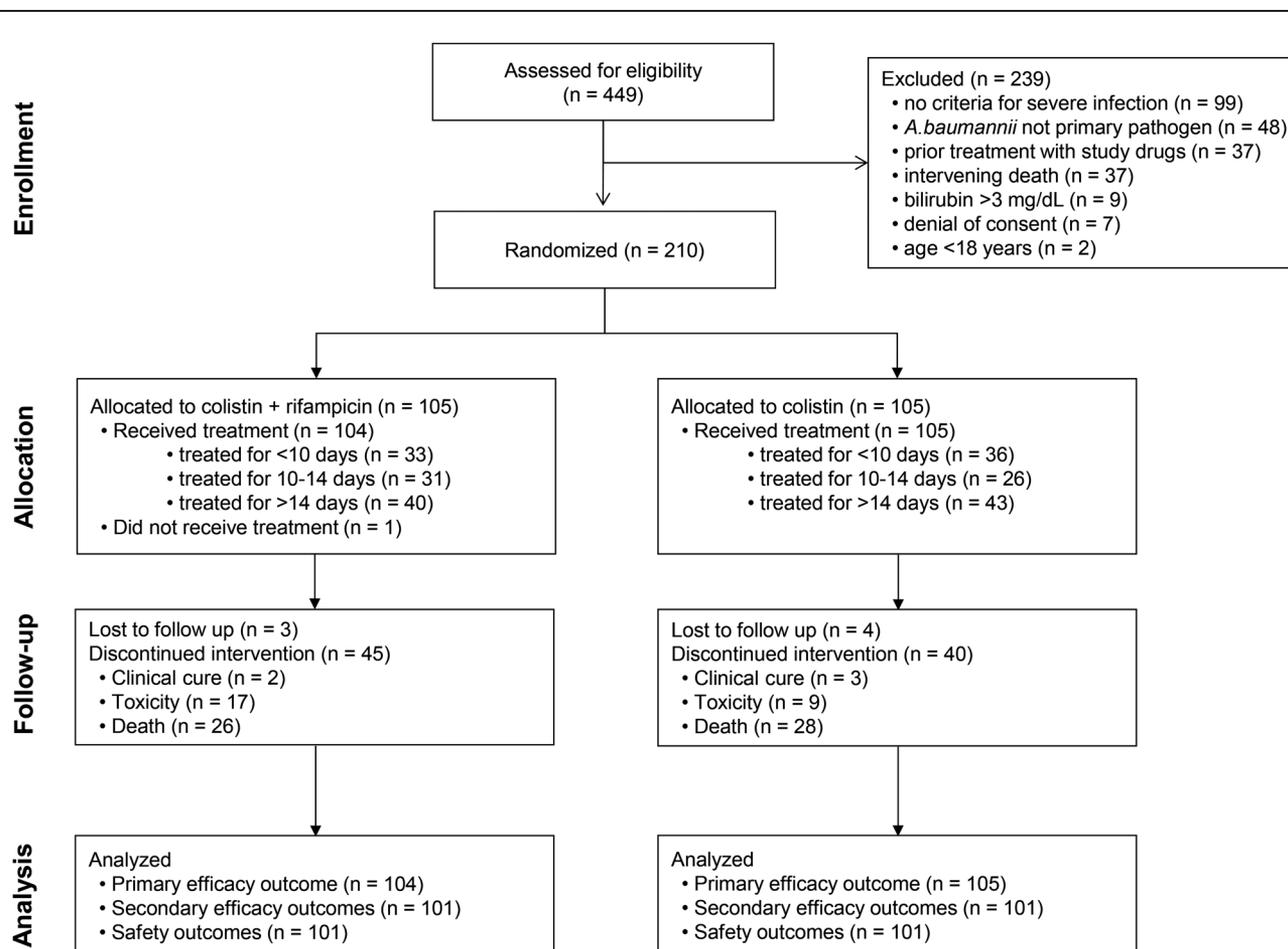

Figure 1. Study flow according to CONSORT statement.

Secondary efficacy outcomes were infection-related death, microbiologic eradication, hospitalization length, and emergence of resistance to colistin during treatment. Because of the study setting (ICU) and the severity of patient conditions, the toxicity assessment was limited to the following adverse events: renal dysfunction and neurotoxicity, possibly related to colistin; and hepatic dysfunction, possibly related to rifampicin.

Sample Size

The study was designed to identify an absolute mortality reduction of 20%. Assuming a raw 30-day mortality rate of 60% in the control group [16, 37], a 2-tailed significance level of .05, a power of 0.8, an allocation ratio of 1:1, and a drop-out rate of 10%, 207 patients had to be enrolled (East software version 4).

Randomization

Treatment was centrally assigned by the coordinating center (Naples University) according to a randomization list prepared in advance by the Medical Statistics Unit, stratified by center and SAPS II score ($\leq$40, >40). Random sequence was generated using random permuted blocks of unequal length. Randomization was performed as soon as Acb was isolated, avoiding delays in active treatment initiation.

Statistical Methods

Efficacy analyses were based on an intention-to-treat strategy. Dichotomous outcomes were compared by χ^2 test, using exact procedures. Odds ratios (ORs), with 95% confidence intervals (CIs), were estimated by a logistic regression model with

Table 1. Baseline Characteristics of the Study Patients

Characteristic	All Patients (n = 209)	Colistin + Rifampicin Arm (n = 104)	Colistin Arm (n = 105)
Age, y, mean (SD)	62 (15.4)	62 (15.1)	61 (15.7)
Male sex	137 (65.6%)	67 (64.4%)	70 (66.7%)
SAPS II score, mean (SD)	39.9 (11.0)	40.8 (10.8)	39.0 (11.1)
Primary diagnosis			
Ventilator-associated pneumonia	144 (69.8%)	71 (68.3%)	73 (69.5%)
Bloodstream infection	42 (20.1%)	21 (20.2%)	21 (20.0%)
Hospital-acquired pneumonia	18 (8.6%)	10 (9.6%)	8 (7.6%)
Complicated intra-abdominal infection	5 (2.4%)	2 (1.9%)	3 (2.9%)
Type of admission			
Medical	42 (20.1%)	20 (19.2%)	22 (21.0%)
Surgical	40 (19.1%)	22 (21.2%)	18 (17.1%)
Emergency/ICU	127 (60.8%)	62 (59.6%)	65 (61.9%)
Comorbidities			
None	29 (13.9%)	14 (13.5%)	15 (14.3%)
Congestive heart failure	48 (23.0%)	22 (21.2%)	26 (24.8%)
Chronic kidney disease	104 (49.8%)	51 (49.0%)	53 (50.5%)
Undergoing dialysis	36 (17.2%)	17 (16.3%)	19 (18.1%)
Diabetes mellitus	49 (23.4%)	22 (21.2%)	27 (25.7%)
Ischemic heart disease	56 (27.7%)	28 (27.7%)	28 (27.7%)
Chronic obstructive pulmonary disease	57 (27.3%)	29 (27.9%)	28 (26.7%)
Cerebrovascular disease/dementia	35 (16.7%)	18 (17.3%)	17 (16.2%)
Obesity (BMI >30 kg/m^2)	41 (19.6%)	20 (19.2%)	21 (20.0%)
Malignancy	22 (10.5%)	11 (10.5%)	11 (10.4%)
Comorbidity index (Charlson)			
0	36 (17.2%)	18 (17.3%)	18 (17.1%)
1	46 (22.1%)	22 (21.2%)	24 (22.9%)
2	58 (27.7%)	31 (29.8%)	27 (25.7%)
$\geq$3	69 (33.0%)	33 (31.7%)	36 (34.3%)
Rifampicin MIC of first Acb isolate			
$\leq$16	160 (76.2%)	78 (75.0%)	82 (78.1%)
>16	43 (20.5%)	23 (22.1%)	20 (19.0%)
Missing	6 (2.9%)	3 (2.9%)	3 (2.8%)

Data are reported as No. (%), unless otherwise specified.

Abbreviations: Acb, *Acinetobacter baumannii*; BMI, body mass index; ICU, intensive care unit; MIC, minimum inhibitory concentration; SAPS, Simplified Acute Physiology Score; SD, standard deviation.

Table 2. Efficacy Outcomes

Outcome	Colistin + Rifampicin Arm (n = 104)	Colistin Arm (n = 105)	P Value
Primary outcome			
30-d mortality			
Yes	45 (43.3%)	45 (42.9%)	.95[a]
No	59 (56.7%)	60 (57.1%)	
Secondary outcomes			
Infection-related death at 30 d			
Yes	22 (21.15%)	28 (26.6%)	.29[a]
No	23 (22.1%)	17 (16.2%)	
Acinetobacter baumannii eradication			
Yes	63 (60.6%)	47 (44.8%)	.034[a]
No	38 (36.5%)	54 (51.4%)	
Median hospitalization length, d (IQR)	41 (26–61)	44 (27–59)	.96[b]
Development of colistin resistance, %	0	0	. . .

Data are reported as No. (%) unless otherwise specified.

Abbreviation: IQR, interquartile range.

[a] Exact χ^2 test.

[b] Log-rank test.

demographic (age and sex) and clinical (source of infection, admission type, concomitant infections, SAPS II score, MIC for rifampicin, comorbidity score) variables as covariates. Interaction between treatment and MIC for rifampicin was also tested. Length of hospitalization was described by reverse Kaplan-Meier curves censoring dead subjects at the time of death [38].

Possible changes of treatment effect among categories of demographic and clinical variables were assessed by Breslow-Day test for homogeneity of odds ratios and depicted as Forest plot. Statistical analyses were performed with Cytel Studio software version 9.0.0 (Cytel Inc).

RESULTS

Patients

Two hundred ten subjects were randomized from 7 November 2008 to 29 July 2011 (Figure 1). One patient did not receive the assigned treatment after randomization and was excluded from all analyses. Seven patients (3 in the experimental arm and 4 in the control arm) lacked complete treatment data because of transfer to other hospitals or long-term care facilities or discharge to home, but were included in the intention-to-treat analyses of the primary outcome as 30-day survival data were obtained.

Main baseline characteristics of the study patients are summarized in Table 1. No imbalances were observed between treatment arms. The most frequent type of infection was VAP.

Table 3. Logistic Regression Analysis of Variables Related to Overall 30-Day Mortality

Parameter	Odds Ratio	95% CI	P Value
Treatment			.71
Col + Rif vs Colistin	0.88	.46–1.69	
Age, y			.37
61–70 vs ≤60	1.47	.64–3.37	
≥70 vs ≤60	1.82	.78–4.22	
Sex			.09
Female vs male	1.82	.92–3.65	
Primary diagnosis			.54
BSI vs VAP	2.02	.62–6.66	
cIAI vs VAP	0.79	.10–6.18	
HAP vs VAP	0.76	.33–1.74	
Admission type			.02
Medical vs emergency/ICU	2.25	.97 – 5.21	
Surgical vs emergency/ICU	3.00	1.24–7.25	
SAPS II score			<.001
>40 vs ≤40	3.38	1.73–6.58	
Comorbidity score (Charlson index)			.008
CI 2–3 vs CI 0–1	1.42	.67–3.01	
CI >3 vs CI 0–1	5.75	1.86–17.77	
Coinfection	0.86	.44–1.69	.66
Rifampicin MIC			.39
>16 vs ≤16	1.43	.63–3.20	

Abbreviations: BSI, bloodstream infection; CI, confidence interval; cIAI, complicated intra-abdominal infection; Col + Rif, colistin plus rifampicin; HAP, hospital-acquired pneumonia; ICU, intensive care unit; MIC, minimum inhibitory concentration; SAPS, Simplified Acute Physiology Score; VAP, ventilator-associated pneumonia.

The majority of patients had been initially admitted to the hospital in an ICU. The median treatment duration was 12.5 days (interquartile range [IQR], 8–17 days). Discontinuation of treatment was mainly due to patient death (Figure 1).

Clinical Outcomes

Efficacy results are reported in Table 2. Death within 30 days from randomization occurred in 90 (43%) subjects (61 during treatment and 29 during follow-up), without any difference between treatment arms (P = .95). The lack of difference between the 2 arms was confirmed by multivariate analysis (Table 3), with an overall OR of treatment equal to 0.88 (95% CI, .46–1.69, P = .71). Type of admission (P = .02), SAPS II score (P < .001), and comorbidity score (P = .005) were significantly associated with 30-day mortality. Mortality was 45.2% in obese and 43.1% in nonobese patients. Odds ratios and 95% CIs for treatment effect are depicted in Figure 2 for patients grouped according to categories of predefined potentially predictive variables. No significant heterogeneity of treatment effect on the primary outcome was observed for sex, age, primary diagnosis of infection, admission type, SAPS II score, Charlson comorbidity index,
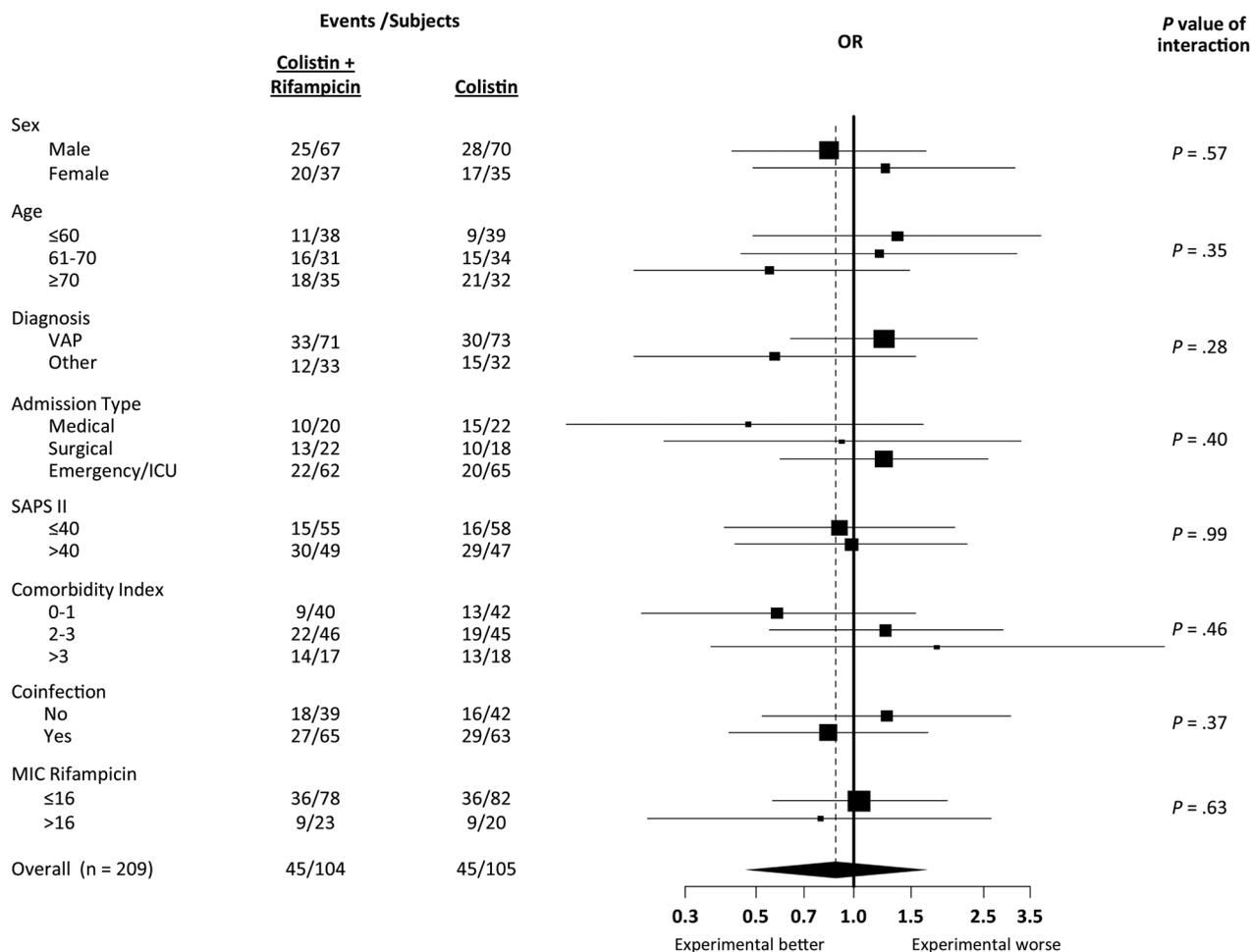
Figure 2. Subgroup analysis of 30-day mortality (Forest plot). The area of each square is proportional to the size of the subgroup; horizontal lines depict 95% confidence intervals of the odds ratio estimates. Abbreviations: ICU, intensive care unit; MIC, minimum inhibitory concentration; OR, odds ratio; SAPS, Simplified Acute Physiology Score; VAP, ventilator-associated pneumonia.

presence of coinfections, and MIC of rifampicin (Figure 2). In particular, no significant interaction between treatment arm and MIC of rifampicin (≤16 vs >16) was detected ($P = .63$). When patients infected with strains showing an MIC of rifampicin >16 were excluded, 30-day mortality rates in the remaining 160 patients were 46.2% in the combination arm and 43.9% in the colistin arm (OR, 1.09; 95% CI, .59–2.04).

Mortality rates in the combination arm and in the control arm were 61.2% and 61.7% respectively, in patients with SAPS II score >40 and 57.1% and 50.8%, respectively, in patients with a Charlson index score >2. In patients with an initial admission in an ICU, death rates were 35.5% and 30.8% in the 2 treatment arms, respectively.

When secondary outcomes were analyzed (Table 2), no difference was observed in terms of infection-related death and length of hospitalization. In contrast, a significant increase of

microbiologic eradication rate was observed in the colistin plus rifampicin arm ($P = .034$). For 7 patients lost to follow-up no information on secondary outcomes was available.

Kaplan-Meier curves of hospitalization length are reported in Figure 3. Median length of hospitalization was equal to 41 days (IQR, 26–61 days) in the experimental arm and 44 days (IQR, 27–59 days) in the control arm.

Colistin MIC was ≤0.5 mg/mL for all Acb isolates at randomization. Resistance to colistin never occurred in any enrolled patient during treatment or follow-up. In contrast, 7 patients randomized to the experimental treatment developed new onset resistance to rifampicin. Of them, 6 (86%) died.

Safety

A summary of toxicities observed in each treatment arm is presented in Table 4. Adverse events were observed in 70 (34.6%)
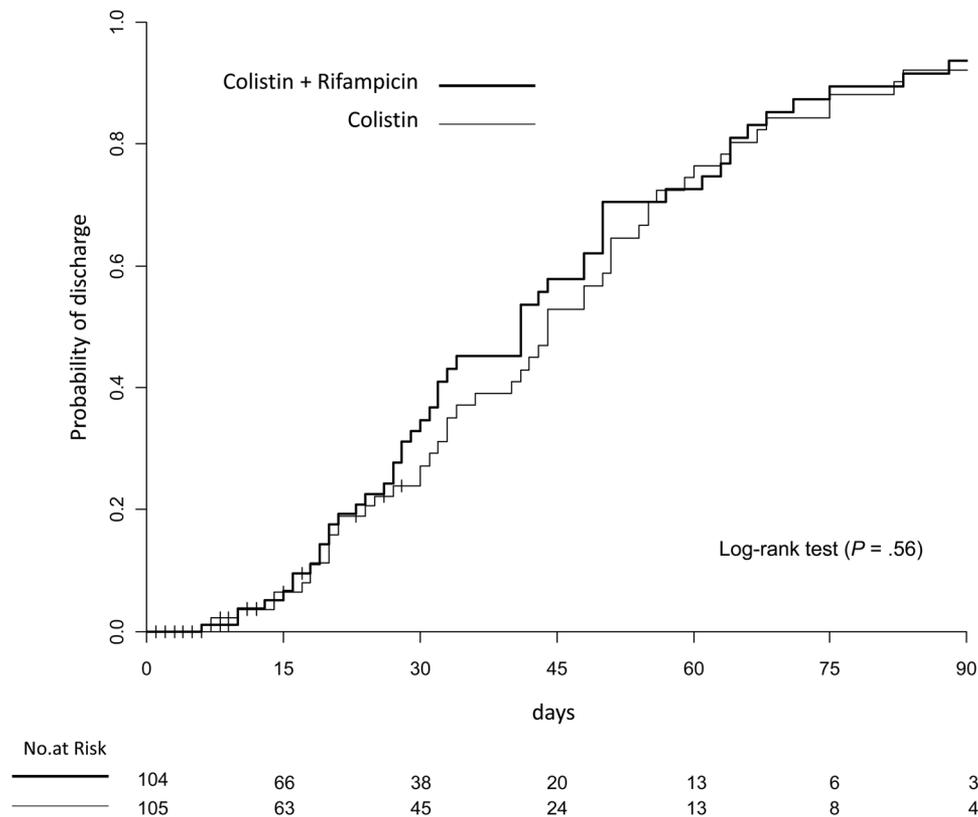
Figure 3. Probability of discharge from hospital by treatment arm (Kaplan-Meier curve).

patients, without differences between experimental and control arm (35.7% and 33.7%, respectively). The most common adverse event was renal impairment, which occurred in 53 patients (26.2%) and led to colistin dose reduction or discontinuation in 17% of patients overall. In 2 subjects (1%), a worsening of renal function leading to renal replacement therapy was recorded. The degree of renal toxicity according to the RIFLE criteria is shown in Table 4. Despite receiving the same initial dose of colistin, underweight patients (body mass index < 18) did not show an increased rate of renal toxicity (3 of 15 [20%]). Liver dysfunction associated with hyperbilirubinemia was more frequent, though not significantly, in the experimental arm, leading to rifampicin dose reduction (9%) or discontinuation (48%) (Table 4). No death was related to the study drug administration.

Coinfections

Concomitant microbial pathogens were isolated in 61% of patients, without differences between treatment arms. Most common copathogens were coagulase-negative staphylococci and *Pseudomonas aeruginosa*. Consistently, concomitant antimicrobial drugs were administered in 145 subjects (69.4%), without differences between treatment arms (67.3% in the experimental arm and 71.4% in the control arm). Appropriate therapy for any concomitant pathogen was administered in all

cases. Meropenem was employed in the control arm more frequently than in the experimental arm (15.9% vs 3.9%), whereas the reverse occurred with tigecycline (4.9% in the control arm vs 10.9% in the experimental arm). These differences were not statistically significant. Details of the other microbial pathogens isolated and the concomitant antimicrobial agents administered are presented in Supplementary Table 2.

DISCUSSION

There is a strong need for randomized controlled trials for the treatment of critically ill patients with infections due to Acb and other nosocomial XDR pathogens [39]. This is the first study evaluating in a randomized fashion the efficacy of colistin and rifampicin combination compared with colistin alone in the treatment of serious infections due to XDR Acb. Our results indicate that 30-day mortality is not reduced by addition of rifampicin to colistin. Moreover, combination treatment affected neither infection-related death nor length of hospitalization.

Interestingly, however, Acb eradication from the primary source of infection was more frequently observed with combination treatment, consistent with previous experimental findings [17–21]. Thus, a potentially beneficial effect of combination treatment

Table 4. Safety Outcomes

Outcome	Colistin + Rifampicin Arm (n = 101)	Colistin Arm (n = 101)	P Value[a]
Renal dysfunction[b]	24 (23.7)	29 (28.7)	.52
Risk	8 (33.3)	13 (44.8)	
Injury	6 (25)	8 (27.6)	
Failure	9 (37.5)	8 (27.6)	
Loss	1 (4.2)	0	
End-stage kidney disease	0	0	
Colistin dose reduction/ discontinuation	8 (33)/9 (37)	6 (21)/9 (31)	
Hepatic dysfunction	21 (20.8)	12 (11.9)	.13
Rifampicin dose reduction/ discontinuation	2 (9)/10 (48)	. . .	
Neurotoxicity	1 (0.99)	0	>.99
Colistin dose reduction/ discontinuation	0/1 (100)	. . .	
Rifampicin dose reduction/ discontinuation	0/1 (100)	. . .	

Data are presented as No. (%).

[a] Exact χ^2 test.

[b] Graded according to the RIFLE criteria: risk, injury, failure, loss, end-stage kidney disease [32, 33].

could be disguised by the inherent complexity of enrolled patients and the severity of their underlying illnesses. Indeed, as previously observed, 30-day mortality was high, irrespective of the treatment received, and was associated with SAPS II score and comorbid conditions, that is, the overall patient clinical status. Consistently, mortality was higher in patients initially admitted in wards other than the ICU, more often affected by chronic medical comorbidities or undergoing surgery for cancer.

The dose of colistin used in this study (2 million units every 8 hours) was chosen based on existing recommendations at the time the study protocol was approved [6, 9–12]. However, the current trend is to use a high loading dose followed by 9 million units per day in 2–3 doses [13, 40, 41]. This regimen is based on novel pharmacokinetic data [42] but is not supported by any randomized trial. In this respect, the potential nephrotoxicity of high-dose colistin is a major concern [13, 43], thus its optimal dosing remains unknown. Of note, using up to 6 million units/day, we observed in this study significant renal toxicity in about 26% of patients, a finding that is consistent with several previous observations showing that colistin nephrotoxicity is dose dependent [32, 33, 43]. We cannot exclude that other factors also played a role in renal impairment.

One issue we explored in detail was the potential effect of rifampicin MIC on combination treatment outcome. Acb

resistance to rifampicin may involve different mechanisms. As recently observed [34], low to intermediate resistance (MICs 4–16 mg/L) appears to be mostly related to altered bacterial membrane permeability, whereas mutations in the *rpoB* gene are associated with high-level resistance (MICs >16 mg/L). Accordingly, and also in agreement with the French Society of Microbiology [36], we used a breakpoint of >16 to define resistance. Theoretically, because colistin impairs bacterial membrane permeability, synergy should be expected mostly in cases due to strains with altered membrane permeability to rifampicin [34]. However, even in the subgroup of patients with MIC ≤ 16, no difference for the primary outcome was observed with combination treatment. As shown by both the interaction analysis and the multivariable analyses (Figure 2, Table 3), rifampicin MIC did not influence the efficacy of combination treatment.

The addition of rifampicin to colistin led to a higher rate of hepatic toxicity. The overall rate of adverse events directly attributable to either colistin or rifampicin was in line with previous findings [32, 33, 43], and there were few serious adverse events and no drug-related deaths.

The observed mortality rate was lower than that considered when the trial was planned (43% rather than 60%). The expected mortality of 60% in the control arm was based on our previous clinical data [37]. Nonetheless, if we assumed a control arm mortality rate of 47% (ie, the mean value reported by a recent review) [44], 175 subjects would be needed to detect the same effect. A potential limitation of this trial was the lack of blinding. However, the pragmatic design and the hard primary outcome made blinding not essential.

In conclusion, rifampicin addition to colistin did not improve survival in serious infections due to XDR Acb. The clinical implication of this finding is that rifampicin should not be added to colistin in clinical practice, at least on a routine basis. The major issue related to Acb treatment remains the current shortage of efficacy data from comparative studies. Attempts have been made to improve colistin efficacy by unorthodox antimicrobial combinations, but none of these proved superiority over colistin monotherapy [14]. As the clinical development of novel antimicrobial agents progresses slowly, any effort should be made to optimize the use of already available drugs. This should only be pursued, however, through adequately powered, randomized clinical trials.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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