Rifampicin Combination Therapies for Colistin-Resistant *Acinetobacter* Spp. in an Intensive Care Unit

Yoğun Bakım Ünitesinde Kolistin Dirençli Acinetobacter Spp. için Rifampisin Kombinasyon Tedavileri

Leyla Talan [1], Neriman Defne Altintas [1], Gulden Yılmaz [2], Goksel Guven [3], Fugen Yoruk [4]

[1]Department of Internal Medicine, Division of Critical Care, Ankara University Faculty of Medicine, Ankara, Turkey
[2]Department of Infectious Diseases and Clinical Microbiology, Gulhane Research and Training Hospital, Ankara, Turkey
[3]Department of Internal Medicine, Division of Critical Care, Tokat State Hospital, Turkey
[4]Department of Infectious Diseases and Clinical Microbiology, Ankara University Faculty of Medicine, Ankara, Turkey

ABSTRACT

Background: There is not a defined therapy for colistin-resistant acinetobacter infections. We aimed to present and discuss the results of ten intensive care unit (ICU) patients who had blood stream infections (BSIs) with colistin-resistant Acinetobacter spp. either pan-resistant (6 patients) or only tigecycline susceptible (4 patients) and who were treated with rifampicin combination regimens.
Methods: Patients who were reported to have BSIs with colistin-resistant Acinetobacter spp. and treated with rifampicin combination regimens were traced from ICU records between years 2014 and 2016, retrospectively. Their demographic data, antimicrobial use, length of ICU stay, SOFA scores, procalcitonin (PCT) levels and ICU outcomes were recorded.
Results: There were a total of 10 patients all of whom had history of colistin use. When blood cultures grew colistin-resistant Acinetobacter spp. rifampicin was added to all patients' existing antimicrobials as salvage therapy. Eight patients improved to ICU discharge. Two patients with higher initial and follow-up SOFA scores were lost.
Conclusions: The treatment of colistin-resistant acinetobacter infections is an unsolved problem in ICUs. When the importance of early accurate antibiotic choice is taken into account in critical patients, adding rifampicin to combination may have some favorable outcomes.

Keywords: Colistin-resistance, *Acinetobacter spp*., bloodstream infection, intensive care unit, rifampicin, combination therapy

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ÖZET

Amaç: Kolistine dirençli *acinetobacter* enfeksiyonları için tanımlanmış bir tedavi yoktur. Kolistine dirençli pan-rezistan(6 hasta) veya sadece tigesikline duyarlı (4 hasta) ve rifampisin kombinasyon rejimleri ile tedavi edilen *Acinetobacter spp*. ile kan dolaşımı enfeksiyonu (BSI) geçiren on yoğun bakım ünitesi (YBÜ) hastasının sonuçlarını sunmayı ve tartışmayı amaçladık.
Yöntem: 2014- 2016 yılları arasında kolistin dirençli *Acinetobacter spp*. bağlı bakteriyemisi olan ve rifampisin kombinasyon tedavisi uygulanan hastalar yoğun bakım ünitesi kayıtları taranarak tespit edildi. Hastaların demografik verileri, antimicrobial tedavileri, yoğun bakım yatış süreleri, SOFA skorları, prokalsitonin düzeyleri ve yoğun bakım sonuçları kaydedildi.
Bulgular: Kolistin kullanım öyküsü olan 10 hasta mevcuttu**.** Kan kültürlerinde kolistin dirençli Acinetobacter spp. üreme olan tüm hastaların tedavisine kurtarma tedavisi olarak rifampisin rifampicin eklendi. Sekiz hasta iyileşti ve yoğun bakımdan taburcu edildi.Kabul ve takibinde yüksek SOFA skoruna sahip iki hasta kaybedildi.
Sonuç: Kolistine dirençli acinetobakter enfeksiyonlarının tedavisi yoğun bakım ünitelerinde çözülmemiş bir problemdir. Kritik hastalarda erken ve doğru antibiyotik seçiminin önemi göz önüne alındığında, kombinasyona rifampisin eklenmesi bazı olumlu sonuçlar doğurabilir.

Anahtar Sözcükler: Kolistin direnci, *Acinetobacter spp*., bakteriyemi, yoğun bakım ünitesi, rifampisin, kombinasyon tedavisi.

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ORCID IDs.L.T. 0000-0003-2023-5985,N.D.A. 0000-0002-7885-8942, G.Y. 0000-0002-2186-492X, G.G. 0000-0002-6916-8907, F.Y. 0000-0001-7487-8439

Address for Correspondence / Yazışma Adresi: Leyla Talan, MD Ankara University Faculty of Medicine, Internal Medicine Department, Critical Care Division İbni Sina Hastanesi ,06100, Altındağ, Ankara, Turkey E-mail: leylatalan@gmail.com

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INTRODUCTION

Acinetobacter spp. is a common healthcare-associated pathogen and is one of the leading causes of intensive care unit (ICU) infections. Patients who had longer ICU stays had higher rates of acinetobacter infections (1,2). Significant resistance to carbapenems among *Acinetobacter* spp. is already reported and in settings with high carbapenem resistance rates, colistin remained the only effective choice. Unfortunately, excessive and prolonged use of colistin also resulted with resistance (3). The emergence of pan-drug resistant (PDR) *Acinetobacter* spp. which is resistant to all classes of available antimicrobial agents including colistin represents a worrying end-point in the development of antimicrobial resistance (4). Colistin combination regimens including rifampicin has been reported against Acinetobacter baumannii infections in multidrug-resistant strains (5). In vitro and in vivo studies have also examined the potential synergy of colistin in combination with rifampicin (6,7).

We aimed to present and discuss the results of our patients who had blood stream infections (BSIs) with colistin- resistant *Acinetobacter* spp., either pan-resistant (6 patients) or only tigecycline susceptible (4 patients) and were treated with rifampicin combination regimens.

METHODS

Patients

The study is a retrospective, uncontrolled case series from the third level ICU's records of a university hospital between years 2014-2016.

Ten patients with the following common features were identified; they were critically ill with BSIs, had longer ICU stays and received colistin on previous infection episodes or they were still on colistin therapy for other resistant gram negative infections. Rifampicin (600 mg/day, po) was added to their existing combination regimens as salvage therapy due to the growth of colistin resistant *Acinetobacter* spp. in blood cultures or the alarm of newly growth of gram negative diplococci which was later reported as colistin-resistant *Acinetobacter* spp.

The study protocol was reviewed and approved by the Ankara University Hospital Institutional Review Board (Approval No. 08-384-16). The need for patient consent was waived due to the retrospective nature of the study.

Definitions

Pan-drug resistance (PDR): Non-susceptibility to all agents in all categories, including colistin. Extensively drug resistance (XDR): Non-susceptibility to at least one agent in all categories except for tigecycline.

Acinetobacter isolates in this study were all resistant to colistin (MIC > 4 mcg/ml) and XDR strains were only susceptible to tigecycline (MIC ≤ 2mcg/ml).

Primary outcome; clinical and laboratory response after adding rifampicin to the combination. Secondary outcome; discharge from the ICU for all patients.

RESULTS

During the study period a total of 10 patients with laboratory confirmed BSIs were determined due to the either PDR (n=6) or XDR (n=4) *Acinetobacter* strains. Patient characteristics were presented on Table 1. Before colistin resistant acinetobacter BSI attack, the mean hospital stay of the patients was 53.4 (30-138) days, and the mean ICU stay was 44.2 (16-130) days. All patients had history of colistin use. Four of 10 patients (patient number 4, 5, 8 and 9) were already on parenteral colistin therapy in combination with tigecycline and/or carbapenem and six patients (patients; 1, 2, 3, 6, 7, 10) were on tigecycline and carbapenem therapy for other gram negative bacterial infections before rifampicin was added to the combinations as salvage therapy. Antimicrobial dosages were as follows; tigecycline; high dose (150 mg/day), colistin; high dose, extended interval with a loading dose of 300 mg colistin base activity followed by 150 mg every 12 hours for patients with normal renal function (10). Meropenem was used as high dose (6 gr/day) extended infusion and rifampicin was used orally (600 mg/day) since no parenteral form was available. Rifampicin susceptibility was not routinely performed for colistin resistant *Acinetobacter* spp.

All colistin MICs were > 4mcg/ml and tigecycline MICs of XDR strains were 0.25 mcg/ml for two isolates (patient number 1, 2) and 2 mcg/ml for the other two isolates (patient number 3, 4).

Table 1. Clinical and microbiological data and combined treatment regimens of patients

Patient	Age	Underlying disease	Length of hospital stay (days)	Length of ICU stay (days)	Resistance pattern	Treatment number (years)
1	63	MM	BSI to VAP	46	25	XDR	M+T+R
2	86	CHF	BSI	56	69	XDR	I+T+R
3	48	Seminoma	BSI	39	31	XDR	M+T+R
		Lung fibrosis					
4	58	ARDS, DM	BSI	36	33	XDR	C+T+R
5	75	COPD, CHF	BSI to VAP	138	134	PDR	C+M+T+R
6	85	CVD, COPD	BSI	35	35	PDR	M+T+R
7	52	MM	BSI to VAP	39	35	PDR	M+T+R
8	67	Pneumonia	BSI to VAP	30	30	PDR	C+T+R
9	63	Scleroderma,ARDS	BSI	58	56	PDR	C+M+R
10	78	Pneumoniae	CLABSI	87	83	PDR	I+T+R

COPD: Chronic obstructive pulmonary disease, CHF: chronic heart failure. ARDS: Acute respiratory distress syndrome, CVD: Cererovascular disease DM: Diabetes mellitus, MM: multiple myeloma,,VAP: ventilator associated pneumonia, BSI: blood stream infection, CLABSI: Central- line associated blood stream infection, M: meropenem, I: Imipenem/cilastatin C: colistin, T: tigecycline, R: rifampicin

All patients were intubated, and 5 of them were on vasopressor therapy. Eight patients survived to ICU discharge and two were lost. Mean initial SOFA score of the 8 survived patients was 11.3 (8-15) and on the 10th day of rifampicin containing regimen, it was 8.8 (3-12). PCT levels regressed during rifampicin combination therapy in patients who survived (Table 2).

Table 2. SOFA scores and procalcitonin levels of patients on the first rifampicin day and thereafter and secondary outcomes

Patient number	SOFA (1st day)	SOFA (10th day)	PCT (ng/ml) (1st day)	PCT(ng/ml) (7th day)	PCT ng/ml) (10th day)	Secondary outcomes
1	22	21	9.07	8.01	8.97	Exitus
2	11	3	0.92	0.6	-	Discharge
3	20	25	20.74	-	-	Exitus
4	10	10	0.77	0.24	-	Discharge
5	15	12	9.92	3.57	1.26	Discharge
6	13	11	10.95	2.17	0.43	Discharge
7	13	11	6.58	0.12	-	Discharge
8	13	12	0.67	0.14	-	Discharge
9	8	7	6.46	0.75	-	Discharge
10	8	5	4.7	0.53	< 0.12	Discharge

PCT : Procalcitonin, SOFA: Sequential Organ Failure Assessment

Initial and follow-up liver enzymes were similar to their basal values and colistin use was cancelled according to renal functions in patients who survived.

When lost patients were re-evaluated; they had higher initial and follow up SOFA scores and no improvement in PCT levels. One of them (patient number 1) had autologous stem cell transplantation for multiple myeloma who had been admitted with acute renal failure and ARDS. *Acinetobacter* spp. isolated from this patient's blood culture showed high colistin resistance (>256 mcg/ml). The second patient (patient number 3) had irreversible lung fibrosis due to bleomycine and was lost with ARDS.

DISCUSSION

According to CAESAR (Central Asian and Eastern Europe Surveillance of Antimicrobial Resistance) data of Turkey; *Acinetobacter* spp. mostly isolated from ICUs which were recovered from blood and cerebrospinal fluid cultures showed 89% carbapenem resistance and 77% multidrug resistance in year 2016 (11). The high resistance rates increased colistin use in our ICUs which in turn resulted as colistin-resistant *Acinetobacter* infections that were much more difficult to treat (3).

There are many reports which tested the efficacy of combination therapies in colistin-sensitive carbapenem-resistant acinetobacter infections including two randomized studies but no significant effect favoring combination either with rifampicin or carbapenem was detected (12-15). Another recent systematic review and meta-analysis showed that combination therapy was not associated with lower mortality for MDR or XDR gram negative infections. However a significant difference favoring combination therapy was observed with high dose colistin, with bacteremic patients, with *acinetobacter* infections and in studies conducted in Asia (16).

Although combination therapy was mostly unfavored in above mentioned colistin-sensitive, carbapenem-resistant acinetobacter infections, we have practically left with no choice when colistin-resistance is in concern. Colistin-resistant *Acinetobacter* spp. occur worldwide showing great geographical variation. The highest resistance rates were reported from Asia and there is no convincing evidence on how to treat these infections in ICUs where colistin-resistant acinetobacter is a major threat (17). The off-label use of high dose tigecycline became prevalent but it did not solve the problem either due to ineffectiveness or side effects. In vitro studies reported synergy with colistin in combination with rifampicin or fosfomycin or vancomycin for colistin-resistant acinetobacter species but clinical data are lacking (6,18).

We have reported the clinical data of 10 ICU patients who had BSIs with colistin-resistant *Acinetobacter* spp. and to whom rifampicin was added to the existing combinations as salvage therapy. Although small in number we think that the results of our patients are important since it provides clinical and laboratory data and these are clinically severe patients with bacteremia. Survived patients were mostly in the PDR group. The two lost patients in the XDR group had the highest initial SOFA scores and one of them showed high colistin-resistance, suggesting that both initial SOFA score and high level resistance might play a role in patient loss. Studies with large patient size are needed to make better suggestions.

The limitations of our study are; it is retrospective, consists of limited number of patients, genome analysis and synergy tests are not performed. In spite of these disadvantages, invasive infections due to colistin-resistant *Acinetobacter* spp. are a great challenge to intensivists and infectious diseases specialists. Although available data do not favor combination therapy, it may be unevitable in XDR or PDR *acinetobacter* infections with colistin-resistance. Adding rifampicin to the combination may have some favorable outcomes.

Conflict of interest

No conflict of interest was declared by the authors.

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