

The Efficiency of Colistin, Minocycline, Tigecycline and Doxycycline against multidrug-resistant *Acinetobacter* strains

The susceptibility of MDR *Acinetobacter* strains

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Abstract

Aim: In recent years, it has been emphasized that antibiotics less used in the past may be an alternative for the treatment of infections caused by multidrug-resistance (MDR) *Acinetobacter* strains. In this study, we aimed to determine the effectiveness of colistin, tigecycline, minocycline, and doxycycline against MDR *Acinetobacter* strains.

Material and Methods: The study was carried out in Samsun Training and Research Hospital in 2018. MDR *Acinetobacter* spp. obtained from 68 patients and reproduced in various clinical samples. Vitec 2 system (BioMerieux, France) was used for the identification of strains and susceptibility testing. The sensitivity of minocycline, tigecycline, and doxycycline was studied in Mueller Hinton agar by Kirby Bauer disc diffusion method. Colistin resistant strains were studied using tube dilution method and minimal inhibitory concentration (MIC) values were determined.

Results: MDR *Acinetobacter* strains were mostly isolated from cultures from tracheal aspirate (32.4%) and wound samples (31.5%). The sensitivity of MDR *Acinetobacter* strains to colistin, tigecycline, doxycycline, and minocycline were 82.4%, 41.2%, 23.5%, 8.8%, respectively.

Discussion: We consider that the sensitivity to colistin is high in MDR *Acinetobacter* spp. infections and that combination of antibiotics, which were used in the past but became less-used later, and other antibiotics can be used for the treatment.

Keywords

MDR *Acinetobacter* spp; Tigecycline; Colistin; Minocycline; Doxycycline

DOI: 10.4328/ACAM.20207 Received: 2020-05-20 Accepted: 2020-06-20 Published Online: 2020-06-30 Printed: 2021-02-01 Ann Clin Anal Med 2021;12(2):120-123

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Introduction

In the last 50 years, multidrug-resistant (MDR) Acinetobacter strains seem to be an increasing cause of death for the patients receiving long-term treatment, intensive care unit patients, burns, and oncological patients. MDR Acinetobacter strains resisting more than three of the available antibiotics might cause different infections such as bloodstream infections, meningitis, ventilator-induced pneumonia, urinary tract infections, skin, and soft tissue infections, and lead to death. These infections can occur in a single patient, or they can easily be transmitted to other inpatients in the service and cause outbreaks. Another important problem is, as Acinetobacter species show intense and widespread resistance to many antibiotics, the treatment of the infections caused by these strains becomes difficult. Over the time, highly resistant species have emerged including XDR (Extreme-drug-resistance) [1,2]. As the infections caused by these factors are increasing, alternative antibiotics that can be used as limited treatment preferences are studied thoroughly. The studies conducted to find sensitive antibiotics became even more important due to the decrease in effective antibiotics, the lack of new antibiotics in treatments and limited antibiotic combinations [1]. Moreover, some antibiotics such as colistin, minocycline, and doxycycline, which have not been used for various reasons for a long time, have come to fore due to high costs and long research period required for finding alternative effective antibiotics for the treatment [2]. Colistin is a toxic drug that has been discontinued due to its side effects. Today, when the number of alternative antibiotics is rapidly depleted, it is planned to use colistin again in treatments after its side effects are reduced. It is emphasized that doxycycline and minocycline, the second-generation tetracyclines, have long serum half-lives, high lipid solubility, low resistance potential, and increased activity against certain pathogens, and like colistin they have been used for a very long time. According to some literature, it is stated that minocycline and doxycycline may be an alternative in the treatment of some infections caused by Acinetobacter spp. [2-4]. Tigecycline, a member of the tetracycline group, is a new alternative antibiotic in the treatment of some infections caused by resistant bacteria [1,2]. However, there are some limitations, such as the resistance developed against minocycline and doxycycline, side effects of colistin, and not being able to use tigecycline against all types of infections. The rapid increase in resistance against existing antibiotics at hand and the inability to launch new antibiotics pushed researchers to seek alternative treatments. In addition to different combinations of various antibiotics, the clinical use of antibiotics such as minocycline, doxycycline, and colistin, which have been out of use for a long time, has come to the forefront. Recently, the effectiveness of these antibiotics against infections caused by MDR Acinetobacter strains has been a matter of question, and researches have been carried out to find out the answer. In this study, we aimed to determine the effectiveness of colistin, minocycline, doxycycline, and tigecycline against MDR Acinetobacter strains.

Material and Methods

This study received approval of the local ethics committee number 2017/24:174. The study was carried out prospectively

at Samsun Training and Research Hospital between January 2018 and December 2018. MDR Acinetobacter spp. strains reproduced in various clinical samples of 68 patients were included in the study.

Bacteria Identification and Evaluation of sensitivity tests

All samples were sown on 5% Sheep Blood agar, Eosin Methylene Blue agar and incubated at 37° C for 18-24 hours. Automatic bacteria identification system, Vitec 2 system (BioMerieux, France) was used for MDR bacteria identification and susceptibility testing. Minocycline and doxycycline susceptibility of Acinetobacter strains were studied by Kirby Bauer disc diffusion method in Mueller Hinton agar. Sensitive strains were determined by working with the tube dilution method with 0.5-16 MIC values. Sensitivity results were interpreted according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST). In our study, A.baumannii ATCC 19606 strain was used as a quality control strain.

Results

Forty-one (60.3%) of the patients included in the study were male and 27 (39.7%) were female. The average age of the study group was 66.2 years. MDR Acinetobacter strains were isolated from cultures collected from tracheal aspirate 35 (32.4%), wound 34 (31.5%), blood 13 (12.0%), sputum 13 (12.0%), urine 11 (10.2) and catheter 2 (1.9) samples.

Samples from which MDR Acinetobacter strains were isolated mostly belonged to patients hospitalized in critical units such as intensive care (69.1%), burn intensive care (8.8%) , and oncological intensive care. The detailed distribution of the samples by clinics is given in Table 1.

The susceptibility of MDR Acinetobacter strains to colistin, tigecycline, doxycycline and minocycline were 82.4%, 41.2%, 23.5%, 8.8% respectively. The susceptibilities of the strains to other antibiotics are given in Table 2. MIC (minimal inhibitory concentration) values of colistin sensitive strains (82.4%) were determined to be between 0.5-2. (Table 3)

Discussion

With the increase of infections caused by MDR Acinetobacter strains, new alternative antibiotics are in great demand for treatment. In recent years, there has been a substantial limitation in terms of the introduction of new alternative antibiotics to clinical use. Although colistin, minocycline, and doxycycline were used in the past, they were abandoned but re-used against resistant bacteria. Tigecycline is a new broad-spectrum antibiotic with gram-positive and gram-negative activity [1]. However, tigecycline resistance was found in some MDR strains. This is caused by the ability of Acinetobacter strains to develop resistance easily [5]. In studies, these antibiotics, which have been interrupted over time and have been investigated as alternatives for resistant cases, have been the subject of research as it is suggested that they might be an option for the treatment of infections caused by MDR Acinetobacter strains [6]. In our study, we have examined whether these antibiotics can be an alternative against MDR Acinetobacter strains isolated from our hospital in order to contribute to this issue. In a study conducted by Wood et al. [3], they stated that seven out of eight cases caused by MDR Acinetobacter strain were successfully

Table 1. Distribution of the clinics of the patients

Clinics	n (%)
Internal Medicine Intensive Care Unit	18 (26.5)
General Surgery Intensive Care Unit	15 (22.1)
Plastic Surgery	11 (16.2)
Burn Intensive Care Unit	6 (8.8)
Oncology Intensive Care Unit	6 (8.8)
Infectious Diseases	4 (5.9)
Internal Medicine	3 (4.4)
General Surgery	3 (4.4)
Neurology Intensive Care Unit	2 (2.9)
Total	68 (100)

n: Number

Table 2. Sensitivities of antibiotics for MDR strains

Antibiotics	n: 68	n	(%)
Colistin		56	82.4
Tigecycline		28	41.2
Amikacin		18	26.5
Gentamicin		18	26.5
Minocycline		16	23.5
Netilmicin		14	20.6
Sulfamethoxazole/trimethoprim		12	17.7
Doxycycline		6	8.8
Imipenem		2	2.9
Meropenem		2	2.9
Ciprofloxacin		2	2.9
Levofloxacin		2	2.9
Ceftazidime		2	2.9
Piperacillin- tazobactam		2	2.9

n: Number

Table 3. Colistin MIC susceptibility rates

MIC	n (%)
0.5	6 (8.8)
1	27(39.8)
2	23(33.8)
4	3(4.4)
8	4(5.9)
16	5(7.3)
Total	68(100)
n: Number	3 (4.4)

treated with minocycline and doxycycline. Griffith et al. [7] stated that in their study, seven of eight patients infected with diseases caused by MDR Acinetobacter strain were successfully treated with minocycline. Liang et al. [4] reported that 100% of meropenem resistant bacteria are sensitive to colistin and minocycline. Chen et al. [8] reported that combined treatments can be used against resistant Acinetobacter strains. In their study, Tan et al. [9] stated that 12 of the 13 MDR Acinetobacter strains responded to colistin and minocycline treatment.

Falagas et al. reported that MDR Acinetobacter strains isolated from different clinical samples have a susceptibility rate between 71.9% and 87.5% against doxycycline, and minocycline in combination with other antibiotics, in their literature study [10]. In these studies, it is emphasized that the sensitivity has increased after the combination of doxycycline and minocycline antibiotics is included. In the studies carried out with doxycycline and minocycline against MDR Acinetobacter strains, various sensitivity rates have been reported in the range of 93.8% to 98.8% , and 72.3% to 84.5% [11-14]. In our study, the sensitivity of minocycline and doxycycline was found out to be 23.5% and 8.8%, respectively. This value was deemed low compared to the studies performed. There was a difference between the sensitivity of minocycline and doxycycline. Studies have shown that tigecycline and colistin are the most effective antibacterials in the treatment of infections caused by MDR Acinetobacter strains [2, 13-15]. Cakirlar et al. from Turkey [16] found the sensitivity of carbapenem-resistant Acinetobacter to colistin and tigecycline to be 100%. In recent studies, sensitivity rates to colistin and tigecycline have been reported as 100% [16-19]. In different studies, MDR Acinetobacter colistin sensitivity rates found to be ranging between 82.5% and 99.8% [13, 20-22], and tigecycline sensitivity rates are found to be in the range of 50.5% and 99.9% [20-24]. In our study, we found the sensitivity to colistin and tigecycline as 82.4% and 41.2%, respectively. These results were interpreted as low compared to the other studies conducted.

In a study, Acinetobacter strains were found to have high resistance to many antibiotics, while their sensitivity to colistin and minocycline was reported as 98.8% and 79.1%, respectively. Also in this study, minocycline was found to be more effective than doxycycline against Acinetobacter strains [16]. Similar results were also emphasized in the study by Siricilla et al. [20]. In our study, the number of doxycycline-sensitive strains was lower than the number of minocycline-sensitive strains. We interpreted this difference as a result of the fact that the routine use of doxycycline is more common than the use of minocycline. In studies carried out using the automated system Vitec 2, colistin sensitivity results have a reliability rate of over 90% [25].

However, EUCAST is suggested to give results with tube dilution MIC detection. In studies, automated systems that detect colistin resistance have been reported to be between 88% and 93%, compatible with microdilution and tube dilution results [25]. In our study, the strains that we found resistant with the automated system were detected with the tube dilution method with 100% accuracy between 0.5 and 2 MIC.

MDR Acinetobacter spp. strains are bacteria with high mortality, which are isolated from critical units over the time and which required us to move quickly at the time of isolation. Since our study covers a certain period of time, the shortage of strains obtained during this period was one of the limiting factors. However, we thought that the results were significant compared to the other studies conducted.

Conclusions

Colistin is the most important alternative in the treatment of infections caused by increasing MDR Acinetobacter species in critical units. In our study, in the light of the literature, we

investigated whether antibiotics, which were in use in the past, but were interrupted later, can be used again as an alternative. However, we believe that combinations of these antibiotics with other antibiotics may create alternative treatments. Tigecycline, on the other hand, is a reliable antibiotic that can be used against diagnoses related to MDR Acinetobacter strains as an alternative to colistin, as it has fewer side effects.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: None

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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How to cite this article:

Selim Gorgun, Murat Guzel, Ozgur Gunal, S. Sirri Kilic. The Efficiency of Colistin, Minocycline, Tigecycline and Doxycycline against multidrug-resistant *Acinetobacter* strains. *Ann Clin Anal Med* 2021;12(2):120-123