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A meta-analysis study on colistin resistance in *Acinetobacter baumannii* species in Turkey

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Abstract

Aim: *Acinetobacter baumannii* is a nosocomial infectious agent that may be resistant to several antimicrobial drugs, including colistin. Colistin is a crucial antimicrobial agent in resistant *A. baumannii* infections. Colistin resistance varies between countries and regions worldwide. This study aimed to evaluate the studies on colistin resistance of *A. baumannii* strains in different regions of Turkey, show the increasing colistin resistance in years, and discuss the solution suggestions.

Methods: The online electronic database was searched for studies evaluating the antibacterial efficacy of colistin combined with other antibiotics or alone in clinical samples of patients with *A. baumannii* infection.

Results: In our study, colistin susceptibility was found to be between 81.8%-100% in Turkey. The lowest susceptibility to colistin for *A. baumannii* strains was reported in the Aegean Region (81.8-100%), followed by Black Sea (82.4-100%), Southeast Anatolia (94-96%), Central Anatolia (95.8-100), Marmara (96.8-100%), Mediterranean (98-100%), respectively, and the highest susceptibility was found in Eastern Anatolia Region (98.6-100%). According to the studies, a partial decrease in colistin sensitivity was found in some regions over the years and more decrease in others, but this decrease was not statistically significant ($p > 0.05$). The cities with the lowest colistin susceptibility were reported as İzmir 81.8%, Samsun 82.4%, Diyarbakır 94%, Düzce 94.1% and Ankara 95.8%.

Conclusion: Colistin is still the most effective antimicrobial drug in *A. baumannii* infections. Our study concluded that there were some differences between regions and even within the same region in colistin susceptibility of *A. baumannii* in Turkey, and resistance development has increased over the years.

Keywords: *Acinetobacter baumannii*; Colistin; Resistance distribution

1. Introduction

Common *Acinetobacter* strains in nature are frequently isolated as an etiological agent in skin, blood, circulatory system, urinary system and other soft tissue infections, and ventilator-associated pneumonia [1,2]. The existing and developing antibiotic resistance to *A. baumannii* is also one of the causes of high mortality rate together with the infection itself

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[3,4]. In recent years, *Acinetobacter* strains were identified as an increasing cause of death in patients receiving long-term treatment in hospital, especially in the intensive care unit, burn units and oncology departments. Infections caused by multi-drug resistant (MDR) and extreme drug-resistant (XDR) *A. baumannii* strains can be seen in a single patient or can be easily transmitted to other patients as outbreaks [2-4]. In this case, combined therapies are used against infectious agents due to the lack of new antimicrobials and the limited alternatives. Colistin has been used for years as an effective drug in treating infections caused by the *Enterobacteriaceae* family and non-fermentative bacteria but as the last choice option due to its side effects. Antibiotics that can be used in the treatment are also limited due to the increasing number of *A. baumannii* infections. The decreased number of effective antibiotics or the absence of new treatment agents, and the limited antibiotic combinations made the existing antibiotics use even more critical [5]. Since carbapenem resistance developed in several cases in recent years, colistin has been used more frequently in the routine, so colistin-resistant strains have increased [6]. Today, colistin is considered the only alternative drug against these strains. Therefore, colistin resistance should be followed up and accurately demonstrated. Various studies have been carried out on the fact that some genotypic changes in *A. baumannii* cause colistin resistance [7]. Indeed, colistin is a toxic drug that has been discontinued due to its side effects. Today, the number of alternative antibiotics is rapidly decreasing, so its reuse is planned by reducing its side effects. Recently, the colistin resistance of *Acinetobacter* strains has been monitored, with each center exhibiting its colistin resistance. However, this information was regional, and the whole country's general view was not clarified. In Turkey, colistin resistance was followed up in some regions in different periods, while very few studies have been performed in others.

This study aimed to examine the studies on the colistin resistance of *A. baumannii* strains in different regions of our country, reveal the increasing colistin resistance in years, and discuss the solution suggestions.

2. Material and methods

This meta-analysis was planned and conducted in line with the recommendations of The European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the Clinical Laboratory Standards Institute (CLSI) regarding the colistin resistance of *A. baumannii* species.

2.1. Search Strategy

The studies in the meta-analysis were screened in PubMed and Google Scholar. During the screening, "*A. baumannii*", "colistin resistance", "Turkey" terms were used in combinations.

2.2. Inclusion Criteria for Studies

Only studies on colistin resistance of *A. baumannii* were included in the meta-analysis. These studies were published or accepted for publication. Case reports were not included in the meta-analysis as they would not contribute significantly to the meta-analysis. Besides, studies or case series with less than 45 patients were excluded from the meta-analysis, affecting data standardization. No language restrictions have been made.

2.3. Article Selection and Data Collection

Titles and abstracts of the selected articles were evaluated in terms of suitability for meta-analysis. Articles outside the scope of the meta-analysis were eliminated. Meta-analyzes were included in this meta-analysis with the thought they would contribute to significant numbers and statistics, but repeated articles and data examined in meta-analyses were excluded. In conclusion, the data of the selected articles were pooled.

2.4. Statistical Analysis

Statistical analyzes were performed by SPSS 25.0 software and online calculators where appropriate. Descriptive data were presented as numbers and percentages. In the study, Spearman correlation analysis was performed for correlation analysis by years. The results were evaluated at a confidence interval of 95%, and $p<0.05$ values were considered significant

3. Results

Following the screening, a total of 44 articles were found worth evaluating. The data in these articles were reviewed by time, regions and provinces. The lowest susceptibility to colistin for *A. baumannii* strains was reported in the Aegean Region (81.8-100%), followed by Black Sea (82.4-100%), Southeast Anatolia (94-96%), Central Anatolia (95.8-100%),

Marmara (96.8-100%), Mediterranean (98-100%), respectively, and the highest susceptibility was found in Eastern Anatolia Region (98.6-100%). (Figure 1, Table 1)

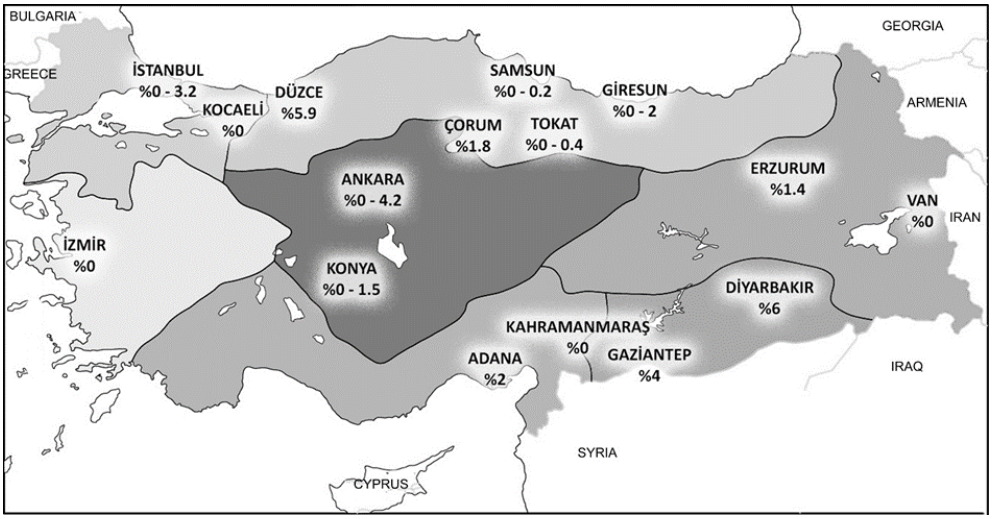

Figure 1 The highest and lowest incidences of colistin resistance on Turkey map by provinces, regions.

The studies showed a more decrease in colistin sensitivity in several regions and a slight decrease in others; however, this decrease was not statistically significant (p>0.05).

Table 1 The distribution of the highest sensitivity rates by regions and correlation analysis by years.

Province	**Year (%)**	**Yıl (%)**	**p**	**r**
Aegean Region	2011 (100)	2013 (81,8)	>0,999	0
Black Sea	2007(100)	2018(82,4)	0,058	-0,866
Marmara	2008(100)	2018(96,8)	0,169	-0,831
Mediterranean	2011(100)	2018(98)	>0,999	0
Central Anatolia	2009(100)	2011(95,8)	0,594	-0,246
Southeastern Anatolia	2012(96)	2011(94)	>0,999	0
Eastern Anatolia	2007(100)	2015(98,6)	>0,999	0

The cities with the lowest colistin susceptibility were reported as İzmir 81.8%, Samsun 82.4%, Diyarbakır 94% Düzce 94.1% and Ankara 95.8%.

Colistin sensitivity in *A. baumannii* strains was reported 100% in the first four years and then 99.8% in Samsun in the Black Sea Region between2006-2011. It was observed that colistin sensitivity decreased in 2018 (82.4%) (p>0.05). No colistin resistance was found in *A. baumannii* strains isolated from Tokat in this region, but it was reported that colistin sensitivity decreased (99.4%) partially in the following years (p>0.05). Colistin sensitivity was 99.2% in Giresun, another city in this region, while 99.5% between 2015 and 2018 (p>0.05). Colistin sensitivity was 98.2% between2012-2013 in Çorum while 94.1% in Düzce between2015-2017, another city in the same region (p>0.05).

Colistin resistance was not reported in *A. baumannii* strains in Ankara in the Central Anatolia region during 2009-2011. The colistin sensitivity was reported in the same city as 93.8-100% between2008-2014 (p>0.05). Colistin resistance was not identified between 2008-2009 and 2011-2013 in Konya, another city in the same region, but colistin sensitivity was reported as 98.6% in a study conducted by a tertiary health institution (p>0.05).

Table 2 The distribution of susceptibility rates of colistin in the studies by cities and correlation analysis by years

City	Year (%)	Year (%)	Year (%)	Year (%)	Yıl (%)	Yıl (%)	p	r
Samsun	2007(100)	2008(100)	2009(100)	2010(99.8)	2011(99.8)		0.058	-0.866
Samsun	2018(82.4)i						-	
Tokat	2007(100)	2008(100)	2009(100)	2010(100)	2011(100)		>0.999	0
Tokat	2016(99.6)	2017(99.6)					>0.999	0
Giresun	2012(99.2)	2013(99.2)	2014(99.2)				>0.999	0
Giresun	2015(100)	2016(98)	2017(100)				>0.999	0
Çorum	2012(98.2)	2013(98.2)					>0.999	0
Düzce	2015(94.1)	2016(94.1)	2017(94.1)				>0.999	0
Ankara	2009(100)	2010(100)	2011(100)				>0.999	0
Ankara	2008(98.6)	2009(98.6)	2011(95.8)	2012(100)	2013(97.7)	2014(98.6)	0.594	-0.246
Konya	2008(100)	2009(100)					>0.999	0
Konya	2011(100)	2012(100)	2013(100)				>0.999	0
Konya	2011(99.5)	2012(98.5)	2013(98.6)				0.391	-0.817
İstanbul	2011(99)	2012(99)					>0.999	0
İstanbul	2014(100)	2015(100)					>0.999	0
İstanbul	2015(99.2)	2016(100)	2017(97.1)	2018(96.8)			0.169	-0.831
Kocaeli	2008(100)	2009(100)	2010(100)	2011(100)	2012(100)		>0.999	0
Kahramanmaraş	2011(100)	2012(100)					>0.999	0
Kahramanmaraş	2012(100)	2013(100)					>0.999	0
Adana	2016(98)	2017(98)	2018(98)				>0.999	0
İzmir	2011(100)						-	
İzmir	2011(100)	2012(100)					>0.999	0
İzmir	2013(81.8)ii						-	
Diyarbakır	2010(94)	2011(94)					>0.999	0
Gaziantep	2012(96)						-	
Erzurum	2014(98.6)	2015(98.6)	2016(98.6)				>0.999	0
Van	2007(100)	2008(100)	2009(100)	2010(100)	2011(100)	2012(100)	>0.999	0

i: The sample group was selected from CID patients only. ii: The sample group consisted only the ventilator-induced pneumonia cases. Spearman correlation analysis was performed.

Colistin sensitivity was reported as 99% in Acinetobacter strains isolated in Istanbul in the Marmara Region between2011-2012. It was reported that colistin resistance was not detected in Acinetobacter strains isolated from patients hospitalized in intensive care units between2014-2015. Again, colistin resistance was not reported in A. baumannii strains isolated from Kocaeli in this region between2008-2012. However, in the same study, colistin sensitivity was determined as 99.2%, 100%, 97.1% and 96.8% in 2015, 2016, 2017 and 2018, respectively ($p<0.05$).

Colistin sensitivity was reported as 100% and 98% in *A. baumannii isolates* between 2011-2012 in Kahramanmaraş in the Mediterranean Region. In Adana, the colistin sensitivity of the *A.baumannii* strain was reported as 98% between the years 2016-2018. No significant increase was found in colistin resistance in this region ($p<0.05$).

Colistin resistance was not found in *A. baumannii* strains in İzmir in Aegean Region between2011-2012. Colistin sensitivity was reported as 81.8% in 2013 in the same region ($p<0.05$).

The colistin sensitivity of *A. baumannii* strain between 2010-2011 in Diyarbakır in the Southeastern Anatolia Region was reported as 94%. A study conducted in Gaziantep in 2012 reported that the colistin sensitivity was 96% ($p <0.05$).

Colistin sensitivity was reported as 100% between 2007-2011 in Van in the Eastern Anatolia Region and 98.6% in Erzurum between2014-2016 ($p<0.05$) (Table 2).

4. Discussion

Colistin resistance in *A. baumannii* infections varies among countries and regions worldwide [8,9]. In a study compiling the data of the Organization for Economic Co-operation and Development (OECD) countries, Xie et al. [10] reported that carbapenem resistance increased approximately three-fold in infections with members of the *Enterobacteriaceae* family and non-fermentative bacteria in 16 years between 2000-2016. In this period, colistin was accepted as the last choice treatment in *A. baumannii* infections [11]. Among the reasons for the changes in colistin resistance performed in different centers in our country, the high comorbidities of patients followed up in intensive care units in cities with high population density, and more extended hospitalization in burns, oncology and neurology intensive care units may be considered.

In Samsun, in the Black Sea Region, Eroğlu et al. [12] conducted a study between 2006-2011 and reported that the colistin sensitivity in *A. baumannii* strains was 100% in the first four years and 99.8% later. Gorgun et al. [13] conducted a study at a different institution in the same region in 2018 and reported that colistin sensitivity of *A. baumannii* strains was 82.4%. In the same years, the *A. baumannii* strains isolated from clinical samples by Savcı et al. [14] in Tokat were found to be sensitive to colistin in the first years but 99.4% in the following years. Şay Coşkun in the same city found the colistin sensitivity against these strains to be 99.6% between 2016-2017 [15]. In the same region, Giresun city, Direkel et al. [16] found the colistin sensitivity of *A. baumannii* strains was 99.2% between 2012-2014, and Uğur et al. [17] found 99.5% between 2015-2018. In Çorum city, Özünel et al. [18] reported colistin sensitivity in the isolated strains of *A. baumannii* 98.2% between 2012-2013, Behçet et al. in Düzce [19] 94.1% between 2015-2017. When the studies conducted over the years in the same province were evaluated by ignoring the differences of the devices used in the laboratories, colistin sensitivity of *A. baumannii* strains seen in Düzce and Çorum, close to major metropolitan cities such as Istanbul and Ankara, and Samsun-the largest city in the region, compared to more distant residential areas decreased slightly even it was insignificant ($p>0.05$).

Colistin resistance rates of *A. baumannii* strains in the Central Anatolia region increased over the years. Şahin et al. [20] reported that they did not detect colistin resistance in *A. baumannii* strains obtained from different hospitals in Ankara between 2009-2011. Hazırolan et al. [21] found in their studies in the same city between 2008-2014 that the colistin sensitivity of *A. baumannii* strains was 93.8-100%. Another city in the same region, Konya, Dağı et al. [22] found the colistin's sensitivity in *A. baumannii* strains isolated from clinical samples was 100% between 2008-2009. Kalem et al. [23] similarly did not detect resistant strains in their study in the same city between 2011-2013. However, Doğan et al. [24] also reported that colistin sensitivity was 98.6% in *A. baumannii* strains isolated from many patients hospitalized in intensive care units in tertiary health institutions between2011-2013 in the same city. The data showed no significant decrease in colistin sensitivity in the same city ($p>0.05$); however, there was some decrease [25]. It may be suggested that this change is essential in the hospital where severe patients are followed up with prolonged hospitalization and comorbid and chronic diseases causing intense antibiotic use.

In Istanbul in the Marmara Region, Iraz et al. [26] found that colistin sensitivity was 99% in the isolated *Acinetobacter* strains between 2011-2012. Barış et al. [27] in Istanbul between 2014-2015; Altunok et al. [28] in Kocaeli in the same region, between 2008-2012, did not detect colistin resistance in their studies. Özekinci et al. [29] reported colistin sensitivity in the *A.baumannii* strains, isolated in several clinical samples as 99.2%, 100%, 97.1% and 96.8%, respectively in 2015, 2016, 2017 and 2018. The four-fold increase in colistin resistance between 2015 and 2018 is remarkable, but this increase was not statistically significant ($p<0.05$).

In the Mediterranean Region, Paköz et al. [30] found in their study conducted in Kahramanmaraş between 2011-2012 that colistin sensitivity of *A. baumannii isolates* was 100%; and 88% if the multi-drug resistant (MDR) *A. baumannii strain* was included. Between 2012-2013 in the same city, Kireşçi et al. [31] reported 100% sensitivity for the strain of *A. baumannii*. In Adana, another city in the same region, Koçak et al. [32] reported that colistin susceptibility was 98% in *A. baumannii* strains isolated between 2016-2018. Although the four-fold increase in colistin resistance between 2015 and 2018 was remarkable, it was not statistically significant ($p<0.05$).

In the Aegean Region, Uzun et al. [33] in 2011, Ece et al. [34] in 2011-2012 reported that colistin resistance was not found in *A. baumannii* strains. Atalay et al. [35] reported the colistin sensitivity as 81.8% in 2013.

In the Southeastern Anatolia Region, Yolbaş et al. [36] conducted a study in a tertiary hospital in Diyarbakır between 2010-2011, and they found that the colistin sensitivity in *A. baumannii strain* was 94%. Karaoglan et al. [37] reported the colistin sensitivity as 96% in 2012 in Gaziantep. However, the decrease in colistin sensitivity in time was not significant in this region ($p<0.05$).

In the Eastern Anatolia Region, Bayram et al. [38] between 2007-2011 in Van found colistin sensitivity 100% in the *A. baumannii* strains isolated from clinical samples. Between 2014-2016, Çelik et al [39] reported that colistin's sensitivity was 98.6% in Erzurum. However, the decrease in colistin sensitivity in time was not significant in this region ($p<0.05$).

Colistin sensitivity of *A. baumannii* strains gradually decreased with region and time. Similar results were obtained in several studies conducted worldwide. A worldwide study with broad participation reported that the sensitivity of colistin gradually decreased over time, and this decrease was higher in Southeast Asia and Eastern Mediterranean countries compared to other parts of the world [40].

Colistin seems to be the most important and only option against the resistant *A. baumannii* strains. Clinicians are concerned about the gradual decrease in the colistin sensitivity over time in the studies. In our country, we are also experiencing an increment in the colistin resistance even it was slow. The resistance rates vary by time, patient group, length of hospitalization, previous antibiotic treatments and hospital classes. Another critical issue is the difference in the tests used to determine the sensitivity of colistin [40-44].

First-step health services should be strengthened to prevent colistin resistance and resistance to all antibiotics and reduce unnecessary or incorrect antibiotic use. Correct methods should be used to determine the colistin resistance of *A. baumannii* strains, and the results should be reported to the relevant clinicians rapidly. Besides, optimal antibiotic guidelines may be formed, considering the differences in colistin resistance detected in *A. baumannii* infections.

5. Conclusion

Although the sensitivity of *A. baumannii* strains to colistin varies according to the regions in our country, it is gradually decreasing. This situation affects the patient's mortality and mobidity. We think that our study will contribute to the use of correct analysis methods and the creation of optimal antibiotic guidelines to determine colistin.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors have no conflicts of interest.

Author Contributions

Opinion, design, analysis, literature review, article writing, revision, approval: SG Analysis, literature review, article writing: MU Analysis, literature review, article writing: HO.

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