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SYSTEMATIC REVIEW – OPEN ACCESS

The War Against the Resistance of *Acinetobacter Baumannii*: A Meta-analysis of Findings in Türkiye

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ABSTRACT

Objective: Bacterial resistance to antibiotics continues to be a significant challenge to the global health system. This study was designed to examine changes in the antibiotic resistance of *Acinetobacter baumannii* (*A. baumannii*) strains isolated from various clinical samples taken between 2005 and 2020 and to support the development of new antibiotics policies for empirical treatment of multidrug-resistant isolates in Türkiye.

Materials and Methods: This meta-analysis included a data search phase, determination of eligibility criteria, qualitative analysis of the studies selected, data extraction, and statistical analyses. All of the data were analyzed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Results: According to Clinical and Laboratory Standards Institute and/or European Committee on Antimicrobial Susceptibility Testing standards and a random effects model, the breakpoint estimate of *A. baumannii* strain resistance in Türkiye for ampicillin-sulbactam, ceftazidime, imipenem, meropenem, gentamicin, amikacin, ciprofloxacin, piperacillin-tazobactam, trimethoprim-sulfamethoxazole, netilmicin, colistin, and tigecycline was 90.7%, 92.1%, 86.8%, 87.3%, 72.6%, 63.7%, 88%, 91.2%, 76.7%, 27.1%, 7.9%, and 18.5%, respectively.

Conclusion: The reported rates of *A. baumannii* resistance from different regions demonstrated heterogeneity. Unfortunately, the use of standard antibiotics is unlikely to provide effective therapy throughout Türkiye. New therapy options and protocols are needed.

Keywords: *Acinetobacter baumannii*, antibiotic, infectious, resistance, treatment

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INTRODUCTION

According to the World Health Organization, *Acinetobacter baumannii* (*A. baumannii*) is a priority pathogen for which innovative therapies are urgently needed (1). This bacterium can cause infections with adverse effects, such as ventilator-associated pneumonia, bacteremia/sepsis, soft tissue infection, urinary tract infection, nosocomial meningitis, peritonitis, osteomyelitis, synovitis, and conjunctivitis (2). The management and control of nosocomial infections caused by *A. baumannii* is difficult due to factors including the long-term survival of bacteria in a hospital environment, rapid spread through contamination, increasing resistance to antimicrobial agents, and a growing number of multidrug-resistant bacterial strains (3). *A. baumannii* has attracted significant scholarly attention, given increases in infection rates, changes in resistance, treatment difficulties, and associated mortality rates among intensive care patients (4).

Carbapenem resistance emerged in the first half of the 2010s, and was soon followed by mutation-induced colistin resistance. This led to a search for alternative therapeutic options. The critical need for innovative therapies, along with a more rapid US Food and Drug Agency approval process based on necessity, has accelerated the development and introduction of new drugs (5). For example, carbapenemase inhibitors, such as ETX2514, WCK 4234, LN-1-255, and zidebactam (WCK 5107) have been introduced in recent years (6).

This study was designed to examine changes in antibiotic resistance among *A. baumannii* strains isolated from various clinical samples collected between 2005 and 2020 and to support the creation of new antibiotic policies to be applied as empirical treatment based on the multidrug-resistant isolates recorded in Türkiye.

MATERIALS and METHODS

Ethic Statements

Ethics committee approval is not required.

The study comprised phases of data collection, determination of eligibility criteria, qualitative analysis of previous studies, data extraction, and statistical analyses. All of the data were analyzed using the method outlined in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (7).

Table 1. Qualitative characteristics used to evaluate the studies

Qualitative characteristics	3 points	2 points	1 point
* Age groups	All age groups	Adult	Children
Number of strains	>200	100-200	<100
Typing method	Automated	Conventional	Undeclared
Antibiotic sensitivity determination	Automated	Conventional	Undeclared
Number of antibiotics evaluated	>10	6–10	<6
Information on clinic and sample	Both	Only one	Undeclared
Antibiotic sensitivity comparison according to sample	Yes	No	Undeclared
Time interval	≥3 years	2 years	1 year

Table 2. Identified antimicrobial groups

Group A	Group B	Group C	Other
Ampicillin-sulbactam (SAM)	Piperacillin-tazobactam (TZP)	Netilmicin (NET)	Levofloxacin (LEV)
Ceftazidime (CAZ)	Trimethoprim-sulfamethoxazole (SXT)	Colistin (CL)	Tobramycin (TOB)
Imipenem (IPM)		Tigecycline (TGC)	Cefepime (FEP)
Meropenem (MEM)			Ceftriaxone (CRO)
Gentamicin (GN)			Cefotaxime (CTX)
Amikacin (AK)			Cefoperazone-sulbactam (SCF)
Ciprofloxacin (CIP)			Aztreonam (AZT)
			Tetracycline (TET)
			Piperacillin (PIP)

Data Collection Strategy

A search was conducted of the PubMed, Web of Science, Turkish Medline, Scopus, EBSCO, and Google Scholar databases for relevant studies published in English and Turkish between January 1, 2005 and December 31, 2020. The search terms used were "*Acinetobacter baumannii*" and "antibiotic susceptibility" and "antibiotic resistance" and "drug resistance" and "antimicrobial drug resistance" and "Turkey" or "*Acinetobacter baumannii*" and "antibiyotik duyarlılığı" and "antibiyotik direnci" and "ilaç direnci" and "antimikrobiyal ilaç direnci" and "Türkiye."

Eligibility Criteria

Conformity with the study goals was initially evaluated based on publication titles and abstracts by 2 independent researchers (IHC and IK). Information such as the authors name, institution where the study was conducted, and the journal in which it was published was disregarded to ensure objectivity. Eligibility criteria for use of a study in the meta-analysis were: the research was conducted in Türkiye, the data presented were obtained between 2005 and 2020, the language of publication was Turkish or English, the papers were original research articles with access to the full text, the statistical data were verifiable in terms of numbers and means, at least 50 strains were examined, and the Clinical and Laboratory Standards Institute (CLSI) or European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints were used to determine antibiotic resistance. In addition, studies that did not provide information about meropenem and/or imipenem resistance were excluded.

Quality Assessment

Each paper was evaluated according to its qualitative characteristics using an assessment chart consisting of 8 questions related to the methods used and the information provided. Each item was given a score between 1 and 3, yielding a total of a minimum of 8 points to a maximum of 24. The total score was used to classify the studies as weak (0–12), moderate (13–18), or strong (19–24) (Table 1).

Data Extraction

Data validation included a thorough check of all reported resistance data to ensure that the classification method was correctly applied. The full text of potentially relevant papers was retrieved and the methodological quality was evaluated. The following information was extracted from the articles that were ultimately included: prevalence rate for the antibiotic resistance of *A. baumannii*, date and year of publication, sample type, sample size, patient gender, clinic details, antibiotic sensitivity comparison, study design (cross-sectional or cohort), and the diagnostic tools and methods used.

All numerical values were recalculated as proportional data in order to collect the antibiotic resistance rates given in the studies as standard units. Antibiotic sensitivity was evaluated according to the Turkish Microbiology Society Antibiotic Susceptibility Test Study Group publication, "Antibiogram Interpretation Criteria and Restricted Notification." Group A includes primary antimicrobials with required testing and reporting, Group B includes secondary antimicrobials with required testing and reporting, Group C includes tertiary antimicrobials with required testing and limited reporting, and the "Other" category comprises other data from the assessed publications (8) (Table 2).

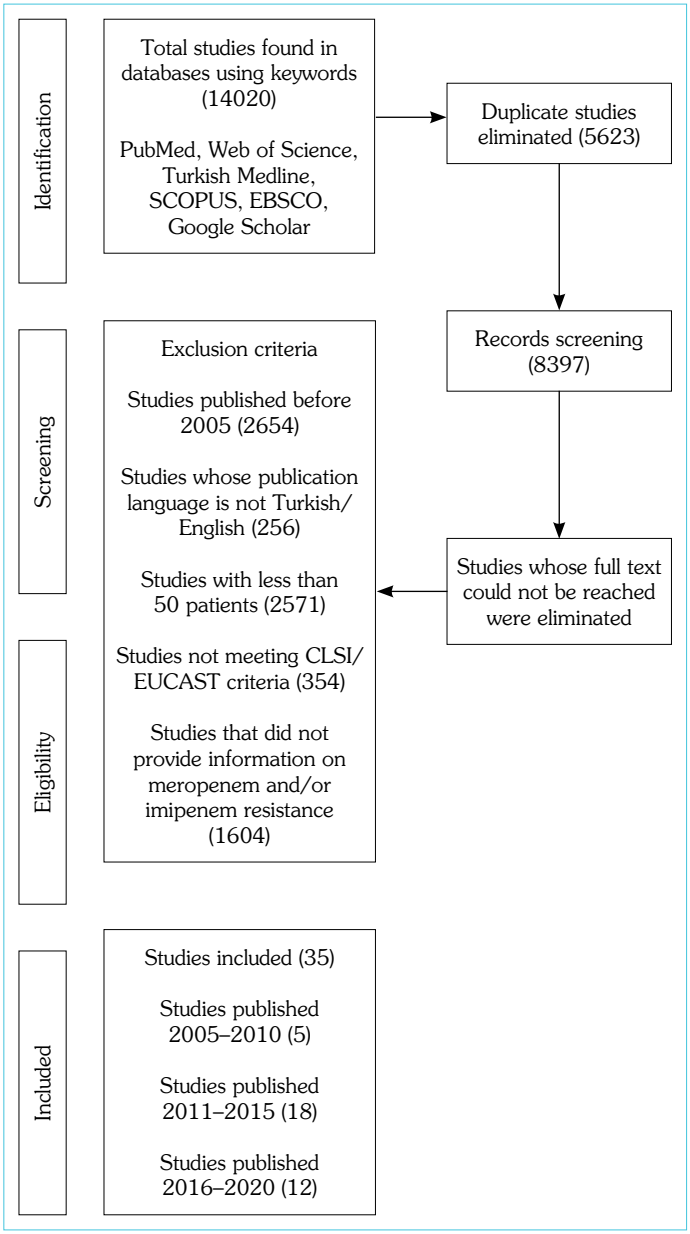

Figure 1. Flow chart of the database search and inclusion criteria

CLSI: Clinical and Laboratory Standards Institute; EUCAST: European Committee on Antimicrobial Susceptibility Testing

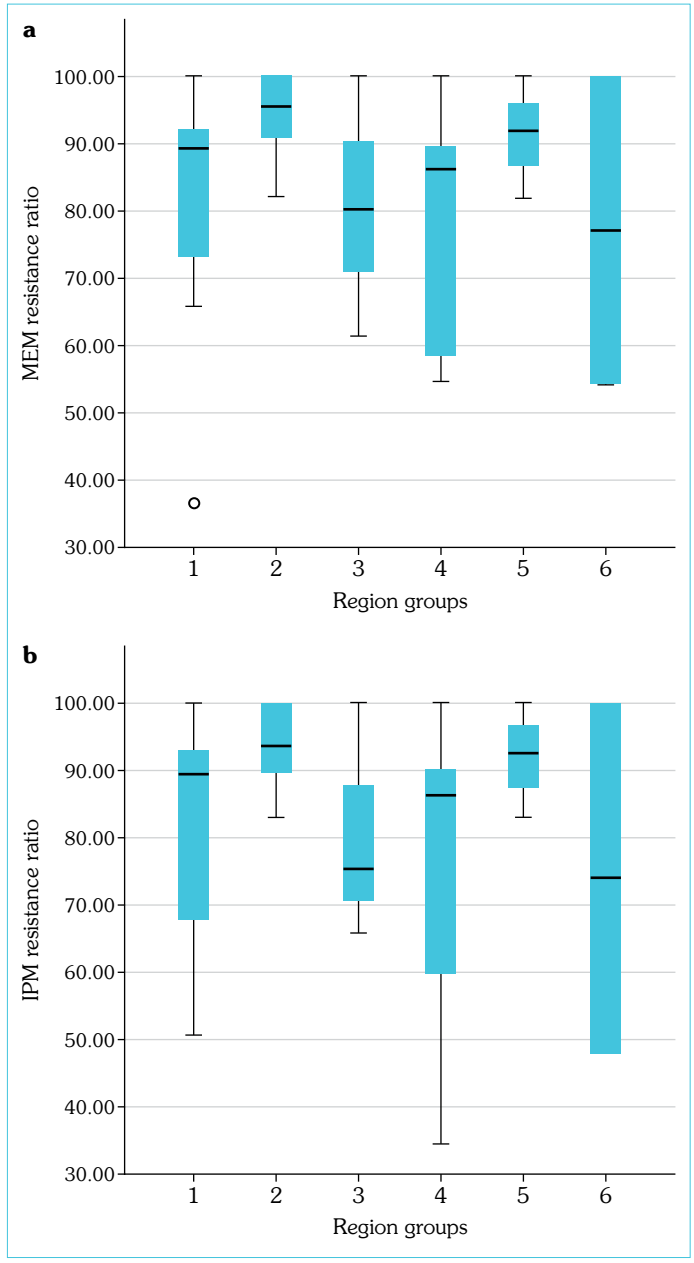

Figure 2. Resistance rate to a) meropenem (MEM) and b) imipenem (IPM) according to region

1: Central Anatolia, 2: Black Sea, 3: Mediterranean, 4: Aegean, 5: Marmara, 6: Southeastern Anatolia

Statistical Analysis

Comprehensive Meta-Analysis (CMA) software (Biostat Inc., Englewood, NJ, USA) was used to calculate pooled estimates of the prevalence of antibiotic resistance in a random-effects model (9). The variance and heterogeneity estimation was modeled using Cochran's Q and I^2 statistics. Values were reported Q, I^2 and p (I^2 <0.250 indicates low heterogeneity, 0.300–0.700 indicates moderate heterogeneity, and >0.750 indicates high heterogeneity) (9). Changes in the antibiotic resistance of *A. baumannii* isolates over time were assessed statistically using IBM SPSS Statistics for Windows Version 26.0 software (IBM Corp., Armonk, NY) using one-way analysis of variance and the Kruskal-Wallis Test. The level of statistical significance was set at p<0.05.

RESULTS

A total of 14020 records were retrieved in the initial database scan; 5623 records were subsequently eliminated as duplicates. The full text of 958 of the remaining 8397 records could not be obtained, and 7439 of the full-text articles were eliminated because they did not meet the other eligibility criteria. In all, 35 studies were evaluated in this meta-analysis (Fig. 1). A total of 6613 *A. baumannii* isolates, 4904 (74.16%) of which were collected in intensive care units, were assessed.

The articles were divided into 3 groups according to the year of publication: 4 articles were published in 2005–2010, 19

Table 3. Change in average antibiotic resistance rates over time (10–43)

Group	Antibiotic	2005–2010 (%)	2011–2015 (%)	2016–2020 (%)	Total (%±SD)	p
A	SAM*	18.98	89.29	94.88	87.96±18.01	0.001
	CAZ*	82.25	60.40	94.57	74.06±40.59	0.088
	IPM*	63.35	83.43	91.17	83.21±17.57	0.008
	MEM*	62.05	84.80	92.91	84.33±16.07	0.001
	GN*	81.56	63.43	79.20	71.11±17.63	0.032
	AK**	57.97	59.19	70.05	62.84±19.98	0.239
	CIP*	59.81	88.29	94.37	86.12±22.39	0.009
B	TZP*	72.52	88.15	93.33	87.78±16.81	0.049
	SXT**	60.72	70.15	78.52	74.27±19.25	0.551
C	NET**	24.18	14.73	50.38	29.28±23.12	0.074
	CL**	6.33	2.94	13.42	6.81±10.51	0.664
	TGC**	11.12	20.65	38.05	24.87±27.76	0.310
Others	LEV**	68.18	84.99	88.82	83.06±15.29	0.152
	TOB**	29.12	38.45	73.47	50.41±24.43	0.155
	FEP*	73.58	88.92	96.83	88.71±18.41	0.071
	CRO**	91.01	66.19	99.39	75.86±34.84	0.343
	CTX**	75.70	93.98	99.69	87.32±26.75	0.058
	SCF*	41.04	72.41	80.61	68.61±20.15	0.008
	AZT**	NA	58.66	99.69	86.02±23.69	0.221
	TET**	60.73	77.51	78.15	74.27±19.26	0.557
	PIP**	90.21	95.09	95.24	94.13±5.46	0.237

*: One-way analysis of variance used to examine the differences in antibiotic resistance by year for normally distributed data; **: Kruskal-Wallis test used to examine the differences in antibiotic resistance rates between year groups among non-normally distributed data; NA: Non-applicable; AK: Amikacin; AZT: Azithromycin; CAZ: Ceftazidime; CIP: Ciprofloxacin; CL: Clindamycin; CRO: Ceftriaxone; CTX: Cefotaxime; FEP: Cefepime; GN: Gentamicin; IPM: Imipenem; LEV: Levofloxacin; MEM: Meropenem; NET: Netilmicin; PIP: Piperacillin; SAM: Ampicillin-sulbactam; SCF: Cefoperazone-sulbactam; SXT: Trimethoprim/sulfamethoxazole; TET: Tetracycline; TGC: Tigecycline; TOB: Tobramycin; TZP: Piperacillin-tazobactam

articles were published in 2011–2015, and 12 articles were published in 2016–2020. Data from multiple years were recorded according to the appropriate year. The studies represented research conducted in 7 regions of the country. The mean quality value was 19.12±0.92 (min–max: 14–22). The strength of 11 of the publications was classified as medium and 23 were graded as strong.

When the resistance change over time was examined, a statistically significant increase was detected for ampicillin-sulbactam (SAM), gentamicin (GN), ciprofloxacin (CIP), imipenem (IPM), meropenem (MEM), piperacillin-tazobactam (TZP), and cefoperazone-sulbactam (SCF) according to the limit values stated in the CLSI or EUCAST guidelines and categorized in Groups A, B, and C. Although there was a noticeable increase in clindamycin (CL) resistance over the years, it did not rise to the level of statistical significance (p=0.664). There were no data for azithromycin (AZT) resistance in 2005–2010. Other data related to resistance rates and the results of the statistical analysis are summarized in Table 3 (10–43).

There has been a significant increase in antibiotic resistance rates in all regions of Türkiye, and the distribution was found to be similar across the Central Anatolia, Black Sea, Mediterranean, Aegean, Marmara, and Southeastern Anatolia regions. The MEM and IPM resistance averages were above 80% in almost all regions (Fig. 2a, b). Due to the insufficient number of reports for netilmicin (NET), CL, tobramycin (TOB), ceftriaxone (CRO), and AZT, statistical analyses regarding regional differences could not be performed. Additionally, an evaluation could not be performed for the Eastern Anatolia region because no articles from that region fulfilled the eligibility criteria.

The studies reviewed revealed some differences in the reports of antibiotic susceptibility or resistance. This is illustrated in column "N" of Table 4. Important heterogeneity between the antibiotic resistance rates for *A. baumannii* was observed across individual studies (I^2 >80%). In the function point (FP) analyses, the estimated resistance rate of *A. baumannii* strains in Türkiye for SAM, CAZ, IPM, MEM, GN, AK, and CIP calculated within the framework of CLSI and/or EUCAST breakpoints in a random effects model (I^2 >80) was 90.7%, 92.1%, 86.8%, 87.3%, 72.6%, 63.7%, and 88%, respectively. The probable resistance rate for TZP, trimethoprim/sulfamethoxazole (SXT), NET, CL, and tigecycline (TGC) in Groups B and C was calculated as 91.2%, 76.7%, 27.1%, 7.9%, and 18.5%, respectively. Other data about breakpoint estimations, lower limits, and upper limits calculated with FP analysis are summarized in Table 4 (10–43).

Table 4. Estimated antibiotic resistance rates of *Acinetobacter baumannii* isolates according to fixed and random effect models (10–43)

Description				Effect size (95% CI)			Heterogenity		
Group	**Antibiotic**	**N**	**Model**	**PE**	**LL**	**UL**	**Q**	**I²**	**p**
A	SAM	19	Fixed effect	0.876	0.857	0.886	520.2	96.5	<0.001
			Random effect	0.907	0.865	0.951			
	CAZ	27	Fixed effect	0.915	0.867	0.950	864.6	96.9	<0.001
			Random effect	0.921	0.916	0.929			
	IPM	35	Fixed effect	0.782	0.770	0.796	785.1	95.7	<0.001
			Random effect	0.868	0.817	0.906			
	MEM	35	Fixed effect	0.797	0.785	0.808	670.4	94.9	<0.001
			Random effect	0.873	0.827	0.908			
	GN	30	Fixed effect	0.683	0.670	0.695	502.8	94.4	<0.001
			Random effect	0.726	0.672	0.774			
	AK	34	Fixed effect	0.623	0.610	0.636	630.3	94.8	<0.001
			Random effect	0.637	0.577	0.692			
	CIP	32	Fixed effect	0.814	0.803	0.826	658.8	95.3	<0.001
			Random effect	0.880	0.833	0.915			
B	TZP	28	Fixed effect	0.863	0.852	0.873	494.5	95.4	<0.001
			Random effect	0.912	0.871	0.941			
	SXT	19	Fixed effect	0.842	0.828	0.856	702.1	97.5	<0.001
			Random effect	0.767	0.661	0.861			
C	NET	8	Fixed effect	0.176	0.158	0.194	343.7	97.6	<0.001
			Random effect	0.271	0.135	0.433			
	CL	9	Fixed effect	0.160	0.135	0.188	60.6	86.8	<0.001
			Random effect	0.079	0.043	0.131			
	TGC	18	Fixed effect	0.166	0.152	0.181	605.2	97.2	<0.001
			Random effect	0.185	0.106	0.302			
Other	LEV	21	Fixed effect	0.826	0.814	0.838	227.1	91.2	<0.001
			Random effect	0.849	0.803	0.886			
	TOB	8	Fixed effect	0.398	0.374	0.423	293.3	97.6	<0.001
			Random effect	0.507	0.393	0.671			
	FEP	25	Fixed effect	0.891	0.881	0.901	184.2	86.9	<0.001
			Random effect	0.906	0.873	0.931			
	CRO	6	Fixed effect	0.843	0.821	0.862	524.4	99.5	<0.001
			Random effect	0.817	0.551	0.974			
	CTX	12	Fixed effect	0.882	0.859	0.902	185.4	94.1	<0.001
			Random effect	0.929	0.839	0.972			
	SCF	14	Fixed effect	0.669	0.648	0.689	324.6	96.1	<0.001
			Random effect	0.695	0.591	0.761			
	AZT	3	Fixed effect	0.885	0.859	0.907	299.1	99.3	<0.001
			Random effect	0.926	0.558	0.969			
	TET	14	Fixed effect	0.821	0.804	0.835	618.3	97.9	<0.001
			Random effect	0.737	0.605	0.847			
	PIP	14	Fixed effect	0.949	0.929	0.958	109.2	88.1	<0.001
			Random effect	0.951	0.939	0.974			

CI: Confidence interval; LL: Lower limit; PE: Point estimate; UL: Upper limit; AK: Amikacin; AZT: Azithromycin; CAZ: Ceftazidime; CIP: Ciprofloxacin; CL: Clindamycin; CRO: Ceftriaxone; CTX: Cefotaxime; FEP: Cefepime; GN: Gentamicin; IPM: Imipenem; LEV: Levofloxacin; MEM: Meropenem; NET: Netilmicin; PIP: Piperacillin; SAM: Ampicillin-sulbactam; SCF: Cefoperazone-sulbactam; SXT: Trimethoprim/sulfamethoxazole; TET: Tetracycline; TGC: Tigecycline; TOB: Tobramycin; TZP: Piperacillin-tazobactam

DISCUSSION

Analysis of the European Surveillance of Antimicrobial Consumption project results revealed high antibiotic usage in 2013 in Türkiye. This finding was converted into a national action plan developed by the Ministry of Health that included quantitative targets on rational drug use (44). This national action plan was directed at all stakeholders and included training, monitoring, and practice guidance. Although the results have not yet been published, the awareness of proper antibiotic usage has been increasing among the Turkish population (45).

However, the increase in antibiotic resistance among bacteria, and especially in cases of nosocomial pathogens, is still a critical problem for the global health system (46). The increased need for intensive care, and especially with the coronavirus 2019 pandemic, has further increased the importance of the fight against infectious nosocomial agents like multidrug-resistant *A. baumannii* (47). It is noteworthy that approximately three-fourths of the *A. baumannii* isolates examined in this study originated in intensive care units; this is an essential warning to take the necessary precautions.

Over the years, resistance rates to antibiotics that are routinely used against *A. baumannii* have increased to over 80%, and the increases in resistance to SAM, GN, CIP, IPM, MEM, PIP and SCF have shown statistically significant differences. The resistance rates for NET, CL, and TIG (50.38%, 13.42%, and 38.05%, respectively), used as alternative treatment agents, are alarming. There is an urgent need to address the increase in the incidence of bacteria resistant to today's antibiotics and the effects of bacterial resistance on public health.

In our statistical analyses, no significant difference was found in the resistance rates to routinely used antibiotics between regions. However, the increase in the resistance of *A. baumannii* to numerous antibiotics over the years and the non-significant differences between the regions are noteworthy. Considering MEM and IPM, in terms of seeing the big picture for the problem of *A. baumannii* resistance (Fig. 2a, b), the reported rates of resistance from different regions demonstrate heterogeneity and, unfortunately, the chances of their use for effective therapy are almost negligible in all parts of Türkiye.

The I^2 value was >94.4% and the possible effect size was >63.7% in the FP analyses performed for the primary antimicrobials defined as Group A, suggesting that the use of these antibiotics for therapeutic purposes poses a great risk for patients across the country. New primary antibiotics that can be used safely are needed. Cefiderocol, which is expected to be approved for clinical use for *A. baumannii* infections, is a new antimicrobial agent that has demonstrated promising in vitro efficacy against large collections of carbapenem-resistant *A. baumannii* strains with various resistance mechanisms (5).

The increase in resistance to TZP over the years and the heterogeneity seen in our data from various regions is also notable. The I^2 value of the secondary antimicrobials defined as Group B was >95.4% and the possible effect ratio was >76.7%. Apart from conventional antibiotic combinations, the success of combined therapy with CL in SXT-susceptible patients highlights the importance of SXT (48). However, the possible effect rate for SXT, calculated to be 76.7% in our study, reduces the possibility of using it as an alternative. The available data show that there is an urgent need for new alternative combinations. Therefore, research on combinations should be given priority and studies in this field should be encouraged. Although no relevant clinical studies were found, there are some candidates for new β-lactamase inhibitors (ETX2514, WCK 4234, LN-1-255, zidebactam, etc.) for use in combinations. These candidates provide hope for the treatment of resistant *A. baumannii* infections (5).

Increased resistance to Group C members, used in compulsory situations due to high doses and toxic effects, is a critical disadvantage that limits treatment options in cases of *A. baumannii* infection (49). We found that the I^2 values were >86.8% and the possible effect size of NET, CL, and TGC was 27.1%, 7.9%, and 18.5%, respectively, in the FP analyses performed for Group C. In light of these data, it can be concluded that the use of members of Group C should be restricted; otherwise, they will cease to be an option for treatment soon. Alternatives such as eravacycline have emerged, but the lack of sufficient data remains the most important reason for limited usage (50).

The "Other" group of antibiotics has no chance of use as a treatment alternative because these antibiotics have significant possible effect sizes and/or ineffectiveness. This is a valuable finding regarding the current state of resistance of *A. baumannii*.

CONCLUSION

Our results highlight the fact that antibiotic resistance rates are high in every region in Türkiye and the need for novel antimicrobials that could be used to successfully control infections caused by *A. baumannii*. To help address this problem, research for new treatment options should be encouraged and *A. baumannii* infections should be monitored for confirmed resistance according to CLSI and/or EUCAST guidelines, clinical information, and molecular epidemiological analysis.

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